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POLYMYALGIA RHEUMATICA[1]

A Clinical Study of 21 Cases

By IAN GORDON

(from Aberdeen Royal Infirmary)

With Plate 38

The purpose of this paper is to draw attention to a rheumatic syndrome which is not widely recognized and occurs mainly in middle-aged and elderly persons. The patient suffers from pain and stiffness in the muscles and periarticular tissues, chiefly in relation to the larger joints of the body. The muscles around both shoulder joints are particularly affected. When the disease has reached its height, muscular and periarthritic pains are more widespread, and movement of joints may then be so limited that the patient is almost completely incapacitated. Characteristically there is a very high erythrocyte sedimentation rate, and hypochromic anaemia is common. General symptoms appear early in the disease—low-grade fever, weakness, anorexia, and loss of weight. Complete recovery appears to take place, usually in two to three years. Salicylates and physiotherapy are of some benefit, but the response to corticosteroid therapy, even in the most severe cases, is most striking. The syndrome has been described under many different names, but until more is known about its cause it is proposed to use the purely descriptive term *polymyalgia rheumatica*, as suggested by Barber (1957). A search of published reports has revealed 140 cases which, from the description of the main clinical features, course, and prognosis, closely resemble this syndrome. Doubtless other cases have been recorded, but because of the diversity of the nomenclature it has not been possible to extract them from the immense volume of writings on rheumatic diseases.

Previously Recorded Cases

Over 70 years ago Bruce (1888), a physician practising at Strathpeffer Spa in Scotland, described five patients (aged 60 to 70 years) who suffered from widespread muscular and joint pains. Recovery took place in one to two years. He named the disease 'Senile Rheumatic Gout' and stated that '. . . these acute senile cases belong to a different category from gout and rheumatism on the one hand and rheumatoid arthritis on the other'. He noted that the disease was remarkable for its severity and complete curability. Meulengracht (1945) recorded two patients suffering from 'humeroscapular periarthrosis, with prolonged fever, loss of weight, and greatly increased sedimentation rate'. The

[1] Received September 10, 1959.

course of the disease was very long, but eventually the patients recovered. In a later study (Meulengracht and Schwartz, 1952) he emphasized the general features of prolonged fever, loss of weight, very high erythrocyte sedimentation rate, and anaemia, in 18 cases of 'periarthrosis humeroscapularis'. Though the rheumatic pains were mainly around the shoulder regions, pains were often initially felt in other parts of the body, and there seems little doubt that his cases belong to the syndrome of polymyalgia rheumatica. The authors stated that the disease was protracted but the final prognosis was good, most patients recovering within two years. Holst and Johansen (1945) described five women, aged 48 to 61 years, with classical features of this syndrome. Pains were around the large joints, chiefly the shoulders and hips, and there was a considerable increase in the erythrocyte sedimentation rate (68 to 100 mm. in one hour); in three patients the temperature was slightly raised for weeks or months. In all cases the disease lasted many months, and considerable improvement was noted, though the patients were observed for periods of only two years or less. They named the disease 'peri-extra-articular rheumatism', and considered it a well-defined clinical entity. Though Porsman (1951) considered that his 29 patients, all over the age of 60, had suffered from a special type of arthritis, there were no demonstrable radiological abnormalities in the joints. The clinical features he described are those of polymyalgia rheumatica; the disease lasted approximately one to one and a half years. In the same year Kersley (1951) described 13 patients (of average age 71) who had an acute onset of severe and widespread muscular pain and tenderness, particularly affecting the scapular muscles and thighs, with raised sedimentation rates, but no signs of arthritis. Loss of weight, fever, and a tendency to anaemia occurred. He thought that what he described as 'a myalgic syndrome of the aged wit ystemic reaction' was probably a rheumatoid syndrome, though none of his cases during the period of observation developed typical polyarthritic deformities. Forestier and Certonciny (1953) recorded a rheumatic syndrome in 25 patients (aged 45 to 79 years) characterized by pains in the scapular and pelvic regions, high erythrocyte sedimentation rates, and systemic symptoms. They claimed that, despite the intensity of the symptoms and the duration of the illness, all the patients had been cured, without sequelae, within two to three years. There were no signs of joint involvement, and they named the disease *pseudo-polyarthrite rhizomélique*. Bevan (1955) described a rheumatic syndrome in three elderly patients with similar clinical characteristics. Anaemia, loss of weight, and fatigue were present, and complete recovery took place in all cases in about 12 months.

It is almost certainly this disease that was described by Bagratuni (1956) when he recorded the clinical features of 21 middle-aged and elderly persons suffering from 'anarthritic rheumatoid disease'. His patients were aged 59 to 82 years, and complained of generalized muscular aching and stiffness, most severe in the neck, shoulders, and back. Fever, sweating, anorexia, loss of weight, anaemia, malaise, and very high erythrocyte sedimentation rates were present. There were no radiographic changes in the joints to suggest active arthritis. He stated: 'no matter how severe the illness may be, the

ultimate prognosis is excellent, although aching and stiffness may persist for months or years with remissions.' These features are characteristic of the syndrome of polymyalgia rheumatica. In some cases Bagratuni recorded abdominal symptoms (flatulence and diarrhoea), headache, cough, skin nodules, and lymphadenopathy; on radiographs of the chest transient shadows were noted in two cases. These findings have not been encountered in the present series, nor have they been mentioned by other authors. In a previous paper (Bagratuni, 1953) he described seven patients (aged 57 to 73) with similar clinical features and good ultimate prognosis. Finally Barber (1957) drew attention to a myalgic syndrome with constitutional effects which he named 'polymyalgia rheumatica'. The ages of his 12 patients ranged from 46 to 68 years. The clinical descriptions, laboratory findings, and clinical course were practically identical with those reported in the present series.

The Present Series

Early clinical features. In the present series there are 21 patients (11 women and 10 men). At the beginning of the disease their ages ranged from 49 to 82 years, the average being 68 years. Prior to the onset all the patients had been in good health and were leading fairly active and well-adjusted lives. Some had essential hypertension, chronic glaucoma, mild angina of effort, or intermittent claudication. In no case was there any evidence of preceding sore throat, respiratory infection, or any obvious psychogenic factors. In most cases the disease struck suddenly. Sixteen patients were able to date the onset of pain and stiffness to within one or two days. Five patients said that their symptoms appeared more gradually. At the start of the disease pain and stiffness were felt around the neck and shoulders, or in the lumbar region, buttocks, or thighs. It was sometimes difficult for patients to remember exactly where symptoms first appeared, since they were not referred to hospital until several weeks after the onset. By this time symptoms had become more widespread. Sometimes a patient stated that pain first appeared in the hip joints, but on closer questioning it was apparent that pain was felt in the adjacent muscles, for example the gluteal or thigh muscles. One patient was able to say that pain was first felt in the right popliteal fossa, and another could locate the initial pain in both deltoid muscles. The sites of pain at the onset were as follows: One or both shoulder regions (six cases), lumbar region or thigh muscles, or both (five cases), lumbar region or buttocks, or both (four cases), back of the neck and shoulder regions (three cases), back of the neck (two cases), right popliteal fossa (one case). In the majority of cases symptoms reached their phase of greatest severity within a month of the onset. In the others progression of symptoms was slower, and the disease did not reach its peak until a few months after the onset.

In the fully developed syndrome pain and stiffness were more widespread, and involved muscles, and to a lesser degree periarticular tissues and tendons,

particularly around the shoulders, elbows, hips, and knees. Movements of the related joints were limited to a degree varying with the severity of the pain. In 12 patients pain and stiffness were so marked when the disease was at its height that they were almost totally incapacitated. Fortunately symptoms of such severity seldom lasted longer than a few months. These patients were confined to the house, or even to bed, and because of limitation of joint movement had great difficulty in dressing themselves and in walking. Two patients were unable to feed themselves for a short time. Others, less severely affected, were able to attend hospital, but could hardly undress without assistance, and found it difficult to climb stairs.

Muscles. Although myalgia often started elsewhere, the muscles of the neck, both shoulder girdles, and upper arms were predominantly affected at some stage in the disease in all 21 cases. Those most commonly involved were the posterior muscles of the neck, the trapezius, deltoid, and biceps. The lumbar, gluteal, hamstring, and quadriceps muscles on both sides were affected in the majority of cases; but pain in these muscles appeared to be generally less marked and less persistent than in the neck, shoulder girdle, and upper limbs. Nevertheless, gluteal and thigh pain was sometimes so troublesome that the patient was almost crippled. In severe cases slight pain was sometimes felt in the triceps, forearm, and pectoral muscles. In one case the pain in both pectoralis major muscles was so marked that it raised the possibility of myocardial infarction. The affected muscles were often slightly tender on palpation, but not invariably so. The muscles below the knee appeared to escape. No nodules were felt either in the muscles or elsewhere.

Periarticular tissues and tendons were also affected by pain and stiffness in the majority of cases, but symptoms were generally less marked than in muscles. Transient stiffness appeared in the fingers in eight cases, and the patients could locate the stiffness to the region of the metacarpophalangeal or proximal interphalangeal joints. One patient complained of aching in front of both wrists for a few weeks. Slight pain in front of an elbow joint occurred in eight cases, and it was clear that pain was felt in the biceps tendon (or its sheath), which was slightly tender to touch. Slight pain and tenderness in front of the shoulder joint was an occasional complaint, but it was difficult to decide whether the capsule of the joint or the long biceps tendon was involved. Tissues around the sternoclavicular joints were painful and tender in two cases, but no swelling was observed. Nine patients complained of pain in the knees, and tenderness could be elicited over the adductor tendons near their insertions, indicating involvement of the tendons or their sheaths. There were also slight pain and tenderness in the popliteal fossa, and sometimes over the quadriceps tendon. No patient felt any pain or aching in the ankles or feet.

Joint swelling. Few authors have recorded swelling of joints. Bagratuni (1956) observed transient joint swelling in four of his 21 cases, and in a previous paper (1953) noted swelling of the wrist in one case. Porsman (1951) mentioned slight swelling of affected joints, but gave no details. In the present series joint swellings, confined to the fingers or knees, were observed in six cases. Unlike

the myalgia, the swellings were of relatively short duration. One patient (Case 12), in the 10th month of the disease, developed pain in and swelling of the metacarpophalangeal joints of the index and middle fingers of the right hand. No treatment other than aspirin was given, and within four months both pain and swelling had disappeared. In the fifth month one patient (Case 21) had a swollen and painful proximal interphalangeal joint of the ring finger of the left hand. The pain and swelling subsided rapidly with prednisone therapy, only to reappear a few weeks after the end of the course. A further course of prednisone caused the symptoms to disappear again, and there has been no recurrence. Four patients developed swelling of both knees, and in three, who were treated by rest and aspirin, the swellings subsided within eight weeks. In the fourth patient swelling of the knees was noted in the eighth month of the disease. By the 13th month, in spite of three courses of corticosteroids given for fairly severe myalgia, a moderate effusion had appeared in the left knee. Aspiration gave a fluid containing large numbers of polymorphonuclear leucocytes and a few mononuclear cells. Without further treatment the swellings had subsided by the 15th month. Advanced osteoarthritis in both knees complicated the clinical picture in this case, and may have been partly responsible for the degree of effusion and its longer duration.

General symptoms. Many of these patients felt ill, and some looked so haggard and dejected as to suggest malignant disease. General symptoms appeared in the first weeks of the disease, and became more noticeable as the myalgia increased. The worse the myalgia, the more marked were the general symptoms, and when pain and stiffness began to abate general symptoms tended to disappear. In the typical case the patient complained of fatigue (20 cases), loss of weight (19 cases), and anorexia (14 cases). Three patients lost as much as two stone in weight. In 12 cases low-grade fever, seldom above 99° to 100° F and sometimes accompanied by sweating, was recorded, and in the more severe cases fever persisted for some weeks. The less severe cases ran an afebrile course, although fever may have been present at the onset of the disease before the patients were admitted to hospital. Insomnia because of pain was common. True depression was not encountered, but many were in despair because they felt sure that they would be crippled for life.

Special Investigations

Erythrocyte sedimentation rate (E.S.R.). One of the most striking and characteristic features of this syndrome is the very high E.S.R. which has been noted in the majority of the recorded cases. In the present series the initial E.S.R. by the Westergren method ranged from 42 mm. to 122 mm. in one hour (average 70 mm.). The E.S.R. fell to lower levels as pain and stiffness abated, and usually remained raised throughout the entire course of the disease. In the later stages of the disease, when only trivial muscular aches persisted, some elevation of the E.S.R. was still a common finding. Corticosteroid therapy led

to a sharp fall to normal or nearly normal readings, which usually rose again soon after therapy was stopped.

Anaemia. Significant anaemia of the hypochromic type was recorded in 13 cases. The initial haemoglobin (Haldane) in six men ranged from 70 to 90 per cent. (9·7 to 12·4 g. per 100 ml.), and in seven women from 60 to 80 per cent. (8·3 to 11 g. per 100 ml.). It was not possible to determine whether the anaemia was a manifestation of the disease or related to the ingestion of aspirin, which had been taken freely by most patients for pain. Stools were tested for occult blood in only a few cases, with negative results except in the case of one woman with a haemoglobin level of 72 per cent. (9·9 g. per 100 ml.), who passed occult blood in the stool during the first week in hospital. In all cases the anaemia improved slowly when oral iron was given, but it was difficult to decide whether or not the response was due to iron, because in some cases the activity of the disease was passing off, and in others corticosteroid therapy was introduced. Anaemia is a common finding in this disease, and has been recorded by Kersley (1951), Meulengracht and Schwartz (1952), and Bagratuni (1956).

Plasma proteins. Total plasma proteins were within normal limits. The plasma globulin was raised to 3 g. per 100 ml. or over in all nine cases in which it was estimated during the active phase, the highest figure recorded being 4·25 g. per 100 ml. As symptoms disappeared the figure fell to normal. In eight cases the plasma globulin was less than 3 g. per 100 ml., but in these patients the estimation was done in the later stages of the disease. Electrophoresis of the serum proteins, when symptoms were severe or moderately severe and before the administration of corticosteroids, showed no constant pattern. Of seven cases in which the investigation was carried out, six showed a slight increase in the α_1- or α_2-globulin fraction, or in both, and three of these cases showed in addition a slight increase in the γ-globulin fraction. In one case the γ-globulin fraction alone was raised to a moderate degree. Bagratuni (1956) has noted similar findings.

Differential sheep-cell agglutination test. The Waaler–Rose test was negative in all 21 cases, and was carried out on more than one occasion in 10 cases. In the 12 cases reported by Barber (1957) the test was also negative. Bagratuni (1956), however, found that five of 14 cases gave a strongly positive reaction (differential agglutination titre 32 or more).

Total leucocyte counts, performed in 16 cases, were within normal limits, as also were differential counts, apart from two cases in which a slight unexplained eosinophilia was found (540 and 440 per cu. mm.).

Other findings which were within normal limits were blood urea and uric acid, serum calcium, phosphate, alkaline phosphatase, and cholesterol, blood culture, Wassermann reaction, agglutinations against *Brucella abortus*, and brucellin skin tests. No abnormal changes were found in the bone marrow in the eight cases in which it was examined.

Radiography of joints did not show any evidence of active arthritis. Osteo-arthritic changes, often affecting the cervical and lumbar spine and less commonly the hips and knees, were seen, but the appearances were those which

one would have expected to find in any group of middle-aged and elderly persons. The osteoarthritis was largely symptomless. In some of the older patients there was mild generalized osteoporosis, but none of the usual radiological changes of rheumatoid arthritis were seen.

Muscle biopsy. In six cases a small portion of deltoid muscle was examined histologically before the start of corticosteroid therapy. In all cases the muscle fibres showed no abnormality, a finding also recorded by Kersley (1951). In the only two cases in which the examination included muscular septa, pathological changes were observed. Case 16 showed 'collections of chronic inflammatory cells in the muscular septa, situated mainly in relationship to dilated vessels with some extension into muscle fibres', and in Case 21 there were 'small collections of lymphocytes arranged in a perivascular manner in both fibro-connective tissue and fat' (Dr. A. Whitley Branwood).

Course and Duration

Patients not treated with corticosteroids. The majority of patients were treated with corticosteroids, but it was possible in the earlier cases, not so treated, to study the natural history of the disease. These cases are considered in some detail, since the increasing use of corticosteroids will in future modify the course of the disease. Eight such patients have now been under observation for periods of up to seven and a half years (six have been studied for five years or more). They were treated in the more severe stages of the disease on orthodox lines, by rest in bed, heat, exercises, and full doses of sodium salicylate or aspirin. These measures gave only slight relief of pain and stiffness, and probably had little effect on the duration of the disease. The effect of phenylbutazone was tried in two cases, with poor response, and one patient received a course of gold salts with no benefit. The disease reached its phase of greatest severity within a few weeks of the onset in six cases, and in four to five months in two.

The course of the disease could conveniently be divided into two stages. In *stage 1* pain was severe (grade 4), moderately severe (grade 3), or slight (grade 2), as shown in Fig. 1. Muscular and periarthritic pain was recorded as severe when patients were almost totally incapacitated, movements of the neck, shoulders, and hips being very painful. They were practically confined to bed, and were unable to dress themselves without assistance. Fortunately, severe pain and stiffness were present in two cases for only two to four months (Cases 1 and 6), and during this period general symptoms were most marked. When pain was moderately severe the patients were ambulant, but joint movement was restricted. Pain was denoted as slight when patients complained of fairly persistent muscular and periarthritic pain, still requiring analgesics for its partial relief. It is admittedly difficult to assess subjective symptoms in a manner such as this, but there is no other satisfactory method of recording the varying severity of the pain during the course of the disease. In the eight cases the first stage of the disease lasted nine to 30 months (average 18 months).

During this stage fluctuations in the degree of pain occurred, but there were no obvious remissions and relapses.

Excluding patient No. 4, who died of myocardial infarction when she had almost completely recovered, *stage 2* of the disease lasted from seven to 25 months (average approximately 15 months), and gradually emerged from the

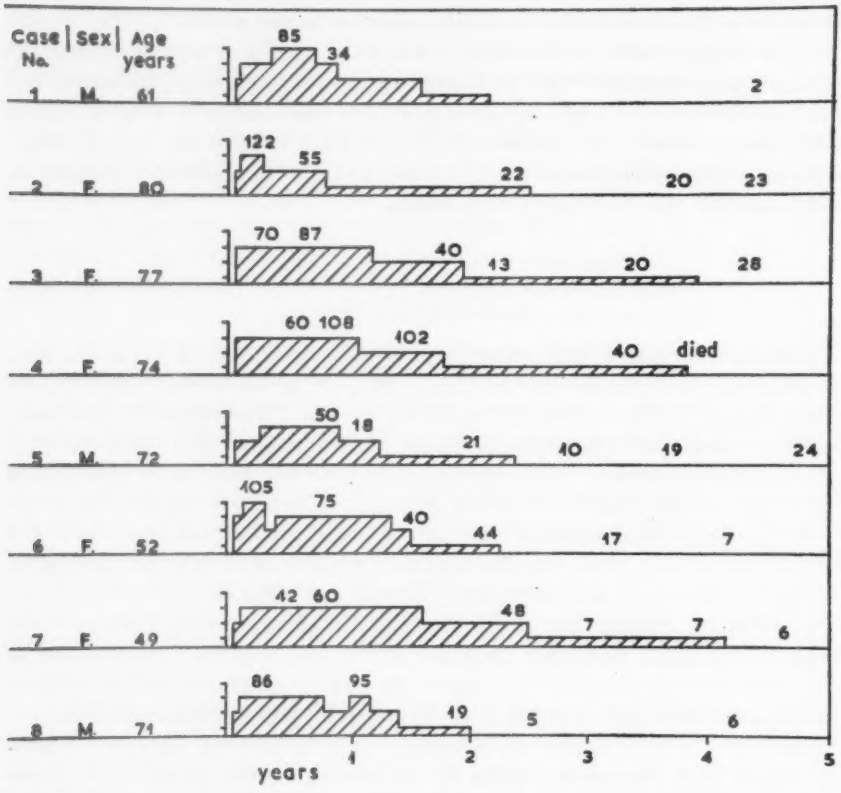
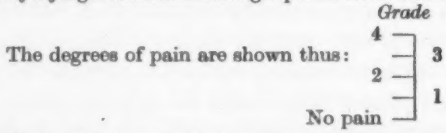


FIG. 1. The course of polymyalgia rheumatica in eight patients not treated with corticosteroids.



The numbers above the hatched areas refer to erythrocyte sedimentation rate readings.

first stage. This stage was one of transient minor aching (grade 1) in the muscles, usually the deltoid, biceps, and triceps, and less commonly the glutei or quadriceps. So slight was the muscular aching that some patients would not have mentioned it unless asked, and often said that they considered themselves cured of the disease. The aching was frequently described as 'nothing to speak of', or 'just an occasional twinge', and was sometimes noticed for a few minutes

after getting out of bed in the morning, when stretching the arms, or when rising from a sitting position. An almost constant feature of this stage was a raised erythrocyte sedimentation rate, which ranged from 13 to 44 mm. in one hour in six cases. In Case 7 the corresponding rate was 7 mm. on two occasions. The persistence of a slightly elevated sedimentation rate, with minor muscular aching, in the later stage of the disease, has also been recorded by Holst and Johansen (1945). Barber (1957) noted that in his cases there was considerable symptomatic relief in spite of evidence of a slightly elevated erythrocyte sedimentation rate.

Excluding patient No. 4, who died of myocardial infarction towards the end of the third year of the disease, the average duration of the disease in seven cases was nearly three years (33 months). The shortest duration was two years, and the longest four years and two months. All seven patients recovered completely, and five have remained free from muscular aching for three years or more. One patient (Case 3) has been free from symptoms for five months, and another (Case 7) for one year. It will be noted (Fig. 1) in Cases 2, 3, and 5 that a raised erythrocyte sedimentation rate persisted after subjective recovery; no explanation could be found.

Illustrative case. Case 6. A 52-year-old woman, the second youngest patient in the series, was admitted to hospital on January 5, 1954. Her illness had started a month previously with pains of fairly sudden onset in the lumbar region and the gluteal and hamstring muscles, more marked on the right side. She complained of fatigue, sweating, and poor appetite, and had lost weight. The muscular pains had so increased in severity that she walked with great difficulty. She looked ill and dejected. Movements of the spine and hips were restricted because of pain, and there was slight tenderness of the affected muscles. Low-grade pyrexia of 99° to 100° F was recorded for six weeks, and there was much sweating at night. When the fever had settled, the systemic symptoms began to lessen. Extensive investigations were made, but the only abnormal laboratory findings were persistently high erythrocyte sedimentation rates (E.S.R.) averaging 105 mm. in one hour (four readings), hypochromic anaemia—the haemoglobin was 72 per cent. (9·9 g. per 100 ml.)—and increased plasma globulin (3·7 g. per 100 ml.). There was no clinical or radiological evidence of joint involvement. She obtained some relief from salicylates and physiotherapy, and was sent home on March 17 after 10 weeks' treatment, much improved but complaining of slight pains in the affected muscles (E.S.R. 55 mm.).

A month later, in April 1954, as pains in the buttocks and thighs lessened, she began to suffer from pain and stiffness in the muscles around both shoulders, and in the muscles of the upper arms and forearms, more marked on the right side. The biceps and deltoid muscles were slightly tender on pressure, as also were the tissues in front of the shoulder joints and the biceps tendons at the elbow. She had great difficulty in abducting her shoulders to 90 degrees. The E.S.R. had risen to 90 mm., and she again complained of fatigue. Heat, exercises, and salicylates were prescribed, and she was able to attend regularly as an out-patient. For a few months she complained of aching and stiffness in the fourth and fifth fingers of the right hand, but at no time was joint swelling observed. After a few months pains and stiffness in the shoulders and arms began to lessen, but persisted for a further year, the duration of the first stage of the disease being 18 months. Eighteen months after the onset she was in

excellent health, and had entered stage 2 of the disease, complaining only of occasional aching in the deltoid muscles; she could fully abduct her shoulders without pain. The aching, which she regarded as trivial, continued for nine months, and during this period (stage 2), the E.S.R. remained raised (30 to 44 mm.). By the end of March 1956, two years and three months after the onset, she was completely free from all aching and stiffness, and has remained so for three years and four months (latest E.S.R. 7 mm.).

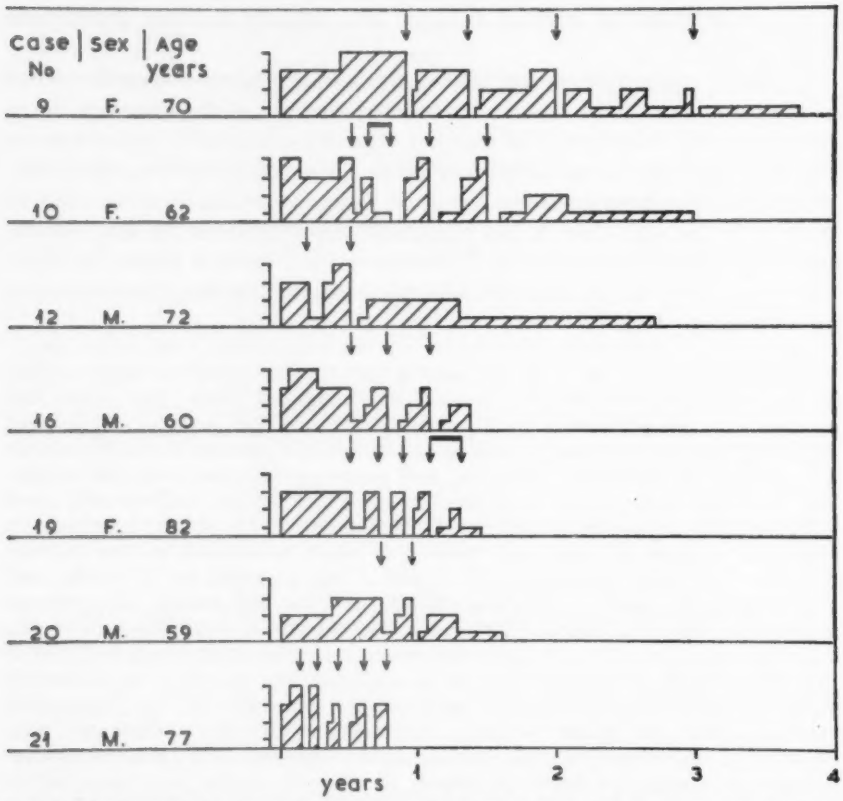


FIG. 2. The course of polymyalgia rheumatica in seven patients requiring two or more courses of corticosteroids. The single arrows indicate the start of each course of prednisone. (The final arrow in Case 10 indicates the start of a course of corticotrophin.) The joined arrows in Cases 10 and 19 each represent a course of prednisone of three months' duration. The degrees of pain are shown by the hatched areas as in Fig. 1.

Patients treated with corticosteroids. Of these 13 patients, when pain and stiffness were severe or moderately severe, 12 were treated with one or more courses of prednisone, one receiving in addition a course of corticotrophin. One was given triamcinolone alone. In every case, if an adequate dose was given, a remarkable and rapid remission of symptoms was induced. Within 48 hours of starting corticosteroid therapy in some cases, and within a few days in others, all pain and stiffness completely or almost completely disappeared (Fig. 2).

In seven patients the symptoms were completely suppressed, and in the remaining six severe or moderately severe pain was reduced to slight and occasional muscular aching. It was most heartening to see a patient, almost completely bedridden before treatment, walking freely round the ward. Movements of the limbs, previously restricted because of pain and stiffness, were now full and painless. The appetite returned, fatigue gave way to a feeling of well-being, and the anxious, despairing facial expression was replaced by one of cheerfulness. A raised temperature of 99° to 100° F, which was recorded in six cases, returned to normal within 48 hours of the beginning of the course of prednisone. As would be expected, there occurred along with clinical improvement a precipitous fall in the erythrocyte sedimentation rate, the readings falling to normal or to slightly above normal.

It was found that an initial dose of prednisone of 30 or 40 mg. daily was required to suppress pain and stiffness. The initial dose was continued in most cases for 10 to 21 days before being gradually reduced. A course usually lasted two to five weeks. In two patients (Cases 10 and 19) a small maintenance dose of prednisone was continued for three months, though complete suppression of pain was not obtained. Recurrence of symptoms of varying degrees of severity, accompanied by a rise in the erythrocyte sedimentation rate, invariably occurred after the end of each course of corticosteroids. In eight cases an exacerbation of symptoms appeared within a few days of the cessation of therapy, and in five cases relapse was delayed for a few weeks. When symptoms in muscles and periarticular tissues did recur, they fortunately often did not regain their former severity. Relapse, however, was sufficiently marked in seven cases to require more than one course of corticosteroids (Fig. 2). One patient (Case 21), one of the most severely affected in the series, had by the ninth month of the disease received five courses of prednisone. Two patients (Cases 9 and 19) were each given four courses of prednisone. Two patients (Cases 10 and 16) had three courses of prednisone, one (Case 10) being given an additional course of corticotrophin; and two (Cases 12 and 20) each received two courses of prednisone. In these seven cases it was noted that after a course of prednisone there tended to be a recurrence of less severe myalgia. From this observation it might be concluded that the prednisone had little or no effect on the duration of the disease, and that its action was merely the suppression of symptoms in the first stage of the disease, when myalgia is more severe. That this was not so is evident from the findings in the remaining six cases, in which a single course of prednisone has so far been sufficient to induce a satisfactory and long remission. Though some recurrence of symptoms occurred in these cases, there was never more than slight tolerable pain (grade 2) or mild occasional aching in muscles (grade 1). These six patients, who have required only a single course of corticosteroids, have been under observation for periods from one to three years. At the time of writing two patients (Cases 11 and 14) are completely free from symptoms. The other four complain only of occasional and transient aching in the biceps, deltoid, or trapezius muscles, and these symptoms are so trifling that the patients might have been regarded as virtually

cured but for the persistence of a slightly raised erythrocyte sedimentation rate, indicating some grumbling activity of the disease. Systemic symptoms have long since vanished. Details are given in Fig. 3. All these patients were treated with prednisone with the exception of No. 15, who was given triamcinolone.

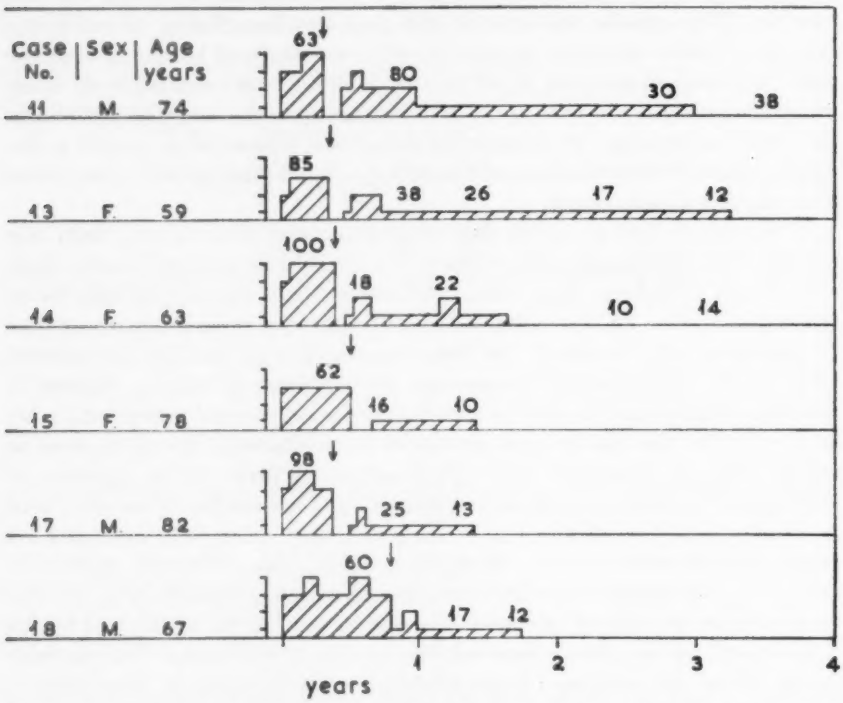


FIG. 3. The course of polymyalgia rheumatica in six patients requiring a single course of corticosteroids, the start of a course being indicated by an arrow. Prednisone was used in all cases except patient No. 15, who received triamcinolone. The degrees of pain and erythrocyte sedimentation rate readings are shown as in Fig. 1.

While the immediate response to prednisone was predictable, it was not possible to foretell which patients would have a relapse of sufficient severity to require further corticosteroid therapy. The occurrence of this type of relapse could not be correlated with the duration or severity of the symptoms before treatment, or with the length of the course of corticosteroids. Indeed, a woman aged 63 (Case 14), who for four months had suffered from the most severe and widespread muscular and periarthritic pains, was completely relieved of her symptoms after a course of prednisone lasting only 16 days. A week later slight muscular pain recurred in her shoulder muscles, and gradually subsided to minor aching. Eight months after the course of prednisone slight muscular pain reappeared, but in three months it again abated to mild occasional aches in her shoulder muscles, which lasted for a further four months. She has remained completely free of symptoms for 18 months.

Discussion

In the early stages of the disease, when only one group of muscles is affected, it is difficult, if not impossible, to reach a firm diagnosis. If the occipital, trapezius, and deltoid muscles are first involved, cervical spondylosis may be simulated, and this mistaken diagnosis may be supported by the presence of positive radiological changes in the cervical spine. It is well known, however, that radiological signs of cervical spondylosis are commonly found in this age group without symptoms. In the present series three patients developed symptoms of cervical spondylosis, but it was not considered that these bore any relationship to polymyalgia rheumatica, since the symptoms occurred when the patients had almost recovered from polymyalgia. In one patient, early in the disease, the sudden onset of pain in the trapezius muscles, with a high erythrocyte sedimentation rate, suggested a diagnosis of nerve-root pressure due to secondary carcinoma of the cervical spine. When myalgia occurs first in the lumbar and hamstring muscles, there will again arise the possibility of nerve-root pressure due to causes such as secondary carcinoma of the lumbar spine and prolapse of a lumbar intervertebral disk. Since the movements of the shoulder joints are so stiff and painful, degenerative periarthritis of the shoulder may be diagnosed, but here the involvement is usually unilateral, constitutional symptoms are absent, and the erythrocyte sedimentation rate is seldom raised. Myelomatosis was suspected in a number of cases because of pain in the back associated with a very high sedimentation rate.

When the syndrome becomes fully developed, with muscular and periarthritic pains more widespread, the clinical picture is more easily recognized. Nevertheless, the combination of myalgia, arthralgia, constitutional symptoms, and high erythrocyte sedimentation rate will raise other diagnostic possibilities, for example, systemic lupus erythematosus or polyarteritis nodosa. Muscle pain may suggest a diagnosis of polymyositis. In the latter disease, however, the muscles are affected by weakness rather than by pain and stiffness; well-marked pathological changes will be found in the muscle biopsy. Carcinomatosis may also have to be considered in view of the systemic symptoms and high erythrocyte sedimentation rate. 'Rheumatism', marked sweating, and lassitude are characteristic features in chronic brucellosis. The rheumatic pains are diffuse, commonly affect the muscles, and are usually associated with stiffness; in some cases pain is localized to joints (Barrett and Rickards, 1953). The muscle pains differ from those of polymyalgia, since they are generally mild and do not predominantly affect the muscles around the shoulders and hips. Moreover, in chronic brucellosis sweating is usually more pronounced, and lassitude is often intermittent, occurring towards the end of the day.

Rheumatoid arthritis will cause much more difficulty, and there is no doubt that there are certain similarities between the two diseases in elderly subjects. Little has been written on the clinical manifestations of rheumatoid arthritis in the elderly, but an authoritative account of this subject has been published by Cecil and Kammerer (1951). In a study of 100 cases of rheumatoid arthritis

which developed in patients at or after the age of 60, they noted three striking features reminiscent of polymyalgia rheumatica. A small percentage showed anaemia, a very high sedimentation rate was a frequent finding (over 40 mm. in one hour in 75 patients), and there was a comparatively large number (55 per cent.) with involvement of one or both shoulders. The authors concluded, however, that apart from these three features rheumatoid arthritis in the elderly did not differ essentially from that seen in younger persons. The small joints of the hands and fingers were the most frequently affected and, if the disease were not arrested, the usual ankylosis and deformity of the joints developed. Similar findings in 50 elderly patients have been recorded by Dordick (1956). It is well known that vague muscle pains, fatigue, lassitude, and loss of weight—the so-called fibrositic prodromal stage—may occur in the early stages of rheumatoid arthritis, before there is much evidence of joint involvement, and may lead to errors in diagnosis. In polymyalgia rheumatica, while fatigue and loss of weight are common symptoms, the muscle and periarthritic pains, unlike those in rheumatoid arthritis, become severe and persist for many months. Swellings of the finger joints have been observed in two cases in the present series, but were transient and have not recurred. Deformities of joints or ankylosis were never observed, nor were erosions or other signs of rheumatoid arthritis seen on numerous X-ray films of the hands and other joints. These negative findings have been stressed in many of the previously reported cases of polymyalgia rheumatica. Further evidence that this syndrome is not rheumatoid arthritis is afforded by the repeatedly negative Waaler–Rose tests in all 21 cases. Finally, the course, duration, and prognosis of the syndrome do not resemble rheumatoid arthritis. It is true that there may occur long remissions in rheumatoid arthritis, but in the present series none of the patients who have recovered has so far shown any signs of relapse.

Long-continued and persistent myalgia in two cases in the series led to such lowering of morale that a tentative diagnosis of psychoneurosis was made before the finding of a raised erythrocyte sedimentation rate. These two cases again demonstrate the need for estimating the sedimentation rate in any middle-aged or elderly patient suffering from myalgia and periarthritic pains (*British Medical Journal*, 1957).

It is clear that a firm diagnosis of polymyalgia rheumatica can be made only after the exclusion of a number of widely differing diseases. It is likely that some *formes frustes* exist, but their recognition will be difficult in the absence of any confirmatory laboratory tests. Nevertheless, the clinical description, laboratory findings, course, and duration of the cases in the present series, and in those previously recorded, conform to a fairly constant pattern, and there now appears to be sufficient evidence to regard the syndrome of polymyalgia rheumatica as a disease *sui generis*. The disease, after a prolonged course, is self-limiting, and does not seem to bear any definite relationship to any other disease. The cause of polymyalgia rheumatica is at present obscure, and the pathological findings of perivascular collections of lymphocytes found in the muscular septa in two cases must be regarded as non-specific. Corticosteroid

therapy induced a remarkable and rapid remission of pain and stiffness, and disappearance of systemic symptoms. None of the 13 patients receiving corticosteroids failed to respond. Kersley (1951) gave three patients short courses of cortisone, and one a course of corticotrophin, and noted an excellent response, with loss of pain and stiffness, and cessation of fever where this was present. Barber (1957) was in no doubt of the immediate response to corticosteroids, but gave few details. It is considered that short courses of corticosteroids, lasting three to four weeks, should be given when necessary, and often one course will be sufficient to induce a satisfactory remission. Long-continued therapy with corticosteroids should be avoided in polymyalgia rheumatica, since pre-existing osteoporosis in elderly patients may be increased, with the danger of collapse of dorsal or lumbar vertebrae.

I wish to thank the physicians and surgeons of Aberdeen General Hospitals and the general practitioners who referred patients to my care.

Summary

The clinical features of 21 cases of polymyalgia rheumatica are described. Middle-aged and elderly persons were affected, and widespread muscular and periarthritic pain occurred, particularly around the shoulders and hips. In the early stages pain and stiffness were often so severe that the patients were almost totally incapacitated. Though transient joint swelling occurred in six cases, there was no radiological evidence of arthritis.

Systemic symptoms were always present. There occurred hypochromic anaemia, increased plasma globulin, and changes in the electrophoretic pattern of the serum proteins, which did not conform to any constant pattern. A characteristic finding was a very high erythrocyte sedimentation rate. The Waaler–Rose test was negative in all cases.

In seven patients not treated with corticosteroids the muscular and periarthritic pains disappeared spontaneously and completely in two to four years, the average duration of the disease being 33 months.

In 13 cases the response to corticosteroids was prompt and striking, pain and stiffness disappearing completely or almost completely within a few days. A long remission was induced after a single course in six patients, pain being reduced to occasional minor aching. In seven patients relapse occurred after the initial course of corticosteroids; these patients required two or more courses of corticosteroids.

In treatment, one or more courses of corticosteroids are recommended rather than long-continued therapy.

The cause of polymyalgia rheumatica is unknown, but it is concluded that there is now sufficient evidence to regard the syndrome as a disease *sui generis*.

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FIG. 4. Case 9. A woman aged 70 attempting a full abduction of her shoulders (*a*) before and (*b*) three days after the start of prednisone therapy

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AN ASSOCIATION BETWEEN ULCERATIVE COLITIS, REGIONAL ENTERITIS, AND ANKYLOSING SPONDYLITIS[1]

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During an epidemiological study of ulcerative colitis and regional enteritis in United States veterans a surprising number of patients were found to have in addition a diagnosis of ankylosing spondylitis (Marie-Strumpell's disease; von Bechterew's disease; rheumatoid spondylitis). This apparent association has been examined in detail, and is reported here.

Material

Data were obtained for all 2,320 male patients discharged from the 174 hospitals of the Veterans Administration[2] with a diagnosis of regional enteritis (572·0), or chronic colitis or enteritis not specified as ulcerative (572·3), during 1953–7, and for ulcerative colitis (572·2) during 1956 and 1957. An additional diagnosis of ankylosing spondylitis (722·1) had been made in 45 cases (Table I), and of rheumatoid arthritis (722·0) in 36. The complete clinical records of all 81 patients were examined and reclassified (Table III), and as a result of this detailed study three of the original 45 cases were discarded, and 12 further cases of ankylosing spondylitis were found, making a total of 54. In doubtful cases X-rays were also studied.

Diagnostic Criteria

1. *Ankylosing spondylitis.* The minimum requirement for a diagnosis of ankylosing spondylitis was radiological evidence of bilateral disease of the sacro-iliac joints, namely loss of definition or irregularity of the joint spaces with subchrondral eburnation. This minimum requirement was fulfilled in 54 cases. In 24 of these cases bilateral obliteration of the sacro-iliac joints had occurred, and in three others there was unilateral or partial obliteration. Since, however, the work of Sharp (1957) and Oates and Young (1959) implied that such changes may occur in other forms of arthritis, the cases have been further classified

[1] Received August 22, 1959.

[2] A veteran is any person who has served in the United States Forces for at least 90 days in war-time. The figures in parentheses refer to the *International Statistical Classification of Diseases, Injuries, and Causes of Death* (sixth revision), 1949.

according to the presence or absence of radiological evidence of disease of the intervertebral (apophyseal) joints and ligaments (Table III). In three cases which had been classified as rheumatoid arthritis, the significance of radiological changes in the neighbourhood of the sacro-iliac joints was doubtful, and they were discarded.

TABLE I

Distribution of the Diagnosis 'Ankylosing Spondylitis' in Patients Discharged from Veterans' Hospitals

	With ankylosing spondylitis		*Total number of cases*
	Number	%	
Patients discharged with various diagnoses, 1953–7:			
Regional enteritis	17	2·3	742
Chronic enteritis not specified as regional	0	0	81
Ulcerative colitis (1956–7)	23	2·0	1,175
Chronic colitis not specified as ulcerative	3	1·4	211
Mixed forms*	2	1·8	111
Total	45	1·9	2,320
Multiple sclerosis (1954)	2	0·2	813
25% sample of Hodgkin's disease (1955–6)	0	0	675
25% sample of all discharges (general medical and surgical beds) 1955–6	227	0·11	205,716

* Ulcerative colitis and regional enteritis together; chronic enterocolitis; ulcerative colitis specified as involving the ileum; regional enteritis specified as involving the colon.

2. *Ulcerative colitis and regional enteritis.* In eight instances the diagnosis of ulcerative colitis had been confirmed by pathological examination of the colon after colectomy or autopsy, and the findings were consistent with those described by Warren and Sommers (1949). In 18 others a history of bloody diarrhoea was supported by sigmoidoscopic evidence of ulcerative or non-ulcerative inflammation of the large bowel satisfying the criteria of Goldgraber, Kirsner, and Palmer (1957); in 12 of these 18 cases a barium enema had also been given with abnormal results. In five other cases a sigmoidoscopy had not been done, and the diagnosis depended on the history of bloody diarrhoea, and on radiological evidence of ulceration, narrowing, or shortening of the large bowel. In one additional instance the diagnosis depended on a barium enema showing only loss of the colonic haustrations; this case was discarded. In 10 cases of regional enteritis a surgical specimen had been examined, and the findings were consistent with those described by Hadfield (1939). In eight others, in which resection had not been performed, the diagnosis depended upon the finding at operation of a thickened or inflamed segment or segments of small bowel. In the remaining four cases the diagnosis was based on clinical and radiological grounds. Three showed Kantor's 'string' sign (Kantor, 1934), and in the fourth there was radiological evidence of extensive involvement of segments of the small bowel by a cicatrizing process. In one additional case (Case 1) there was pathological proof of the coexistence of ulcerative colitis and regional enteritis in the presence of ankylosing spondylitis.

Results

Table I shows the distribution of 45 cases of ankylosing spondylitis in 2,320 cases of chronic colitis and enteritis, according to the diagnosis appearing in the clinical summary, before examination of the records in detail. For comparison the number of cases in which ankylosing spondylitis had been diagnosed in veterans discharged with multiple sclerosis in 1954 is also given. This information was derived from summary sheets in the same way as for enteritis and colitis, and was not corrected by a detailed survey. In addition, the Table gives figures derived from a systematic 25 per cent. sample of (1) all discharges

TABLE II

Age Distribution of the Diagnostic Groups used in Table I

Age in years on admission to hospital	*Age distribution (percentages) of veterans with various diagnoses*				
	Regional enteritis	*Hodgkin's disease*	*Ulcerative colitis*	*Multiple sclerosis*	*All medical and surgical discharges*
Less than 24	18	10	5	4	4
25–34	39	38	40	40	18
35–44	21	31	32	38	22
45–54	4	5	10	8	12
55–64	13	12	12	8	24
65+	5	4	1	2	20

from Veterans Administration hospitals for the period 1955–6, and (2) all discharges from those hospitals of patients with Hodgkin's disease within the same period. The diagnosis 'ankylosing spondylitis' occurred about 20 times as frequently in patients with ulcerative colitis and regional enteritis as in all patients discharged from Veterans Administration hospitals, or in patients discharged with multiple sclerosis or with Hodgkin's disease. The age distribution, expressed in percentages of the five main groups of cases used in Table I, is shown in Table II. It can be seen that the age distribution of regional enteritis is similar to that of Hodgkin's disease, while that of ulcerative colitis resembles that of multiple sclerosis. The bimodal pattern reflects the effect of two world wars on the age pattern of the veterans population.

As a result of a detailed study of the clinical records and X-rays, 17 of the 45 original patients were found to have regional enteritis, 24 ulcerative colitis, and one both ulcerative colitis and regional enteritis (Case 1). In the other three cases the diagnosis of 'chronic colitis not specified as ulcerative' (Table I) was inadequately based, and they were omitted. The 42 remaining patients were found to have evidence of ankylosing spondylitis as defined. In addition, a study of the records of the 36 patients with a diagnosis of rheumatoid arthritis revealed 12 more cases of ankylosing spondylitis (as has already been mentioned, three other cases with doubtful evidence of disease of the sacro-iliac joints were discarded), five associated with regional enteritis and seven with ulcerative colitis. This surprising finding is doubtless due to the policy in the United States, which is approved by the American Rheumatism Association (McEwen,

Ziff, Carmel, Ditata, and Tanner, 1958), of classifying ankylosing spondylitis as a variant of rheumatoid arthritis. Table III shows the frequency of radiological evidence of spinal involvement (disease of the apophyseal joints, calcification of ligaments, or both) and of associated findings, in each group. In addition,

TABLE III

The Distribution of Joint Disease and Uveitis in 54 Cases of Ankylosing Spondylitis Associated with either Ulcerative Colitis or Regional Enteritis, or Both

	Bilateral sacro-iliac disease		*Associated findings*		
	Without radiological evidence of spinal involvement	*With radiological evidence of spinal involvement*	*Disease of hips or shoulders*	*Symmetrical involvement of peripheral joints*	*Uveitis*
Regional enteritis	9	13	7	3	4
Ulcerative colitis	13	18	4	5	5
Ulcerative colitis and regional enteritis	0	1	0	0	0
Total	22	32	11	8	9

TABLE IV

The Interval in Years Between the Onset and Diagnosis of Ankylosing Spondylitis, and of Ulcerative Colitis or Regional Enteritis

Case 1 is omitted from this table

	Interval in years	*Diagnosis*		*Approximate onset*	
		Ulcerative colitis	*Regional enteritis*	*Ulcerative colitis*	*Regional enteritis*
Ankylosing spondylitis before ulcerative colitis or regional enteritis	20+	0	2	1	3
	10–19	2	2	5	2
	5–9	3	4	6	8
	1–4	5	3	5	3
	Less than 1	2	2	2	1
	Synchronous*	12	1	7	2
Ulcerative colitis or regional enteritis before ankylosing spondylitis	Less than 1	0	0	0	0
	1–4	5	5	2	0
	5–9	0	3	0	0
	10–19	1	0	1	0
	20+	1	0	1	0
	Total	31	22	30	19
	Dates unknown	0	0	1	3

*During the same stay in hospital.

there was clinical evidence (a minimum of back pain, and limitation of spinal movement) of involvement of the spine, without radiological evidence, in 11 patients. Twenty-four patients (14 with ulcerative colitis, nine with regional enteritis, and one with combined disease) showed the classic picture of advanced spondylitis with obliteration of the sacro-iliac joints, extensive ankylosis of the intervertebral joints, marked kyphosis, and reduced chest expansion. Nine patients, five with ulcerative colitis and four with regional enteritis, had suffered from uveitis during their illness.

Table IV indicates the time interval between the development of the two types of condition. In view of the inherent inaccuracy in determining dates of onset from case records, the intervals between the diagnoses of the conditions are also given. It is noteworthy that, in 17 of 19 cases in which sufficiently detailed information was available, symptoms of spondylitis preceded those of regional enteritis, although a definite prior diagnosis of spondylitis had been made in only 13. In ulcerative colitis, symptoms of spondylitis had preceded the onset of diarrhoea in 19 of 30 cases, and a firm prior diagnosis had been made in 12. This finding is contrary to the evidence in published reports. According to Steinberg and Storey (1957), McEwen, Ziff, Carmel, Ditata, and Tanner (1958), and Fernandez-Herlithy (1959), ulcerative colitis usually precedes the development of spondylitis. In two instances evidence of ankylosing spondylitis was noted incidentally on the preliminary film of a barium enema given because of ulcerative colitis. A history of backache was then sought and obtained, although the significance of symptoms elicited by direct questioning in such circumstances is open to doubt.

It was felt important to examine any possible relationship between irradiation for spondylitis and the subsequent development of either abdominal disease. Deep irradiation had been given in 14 cases, but in eight of these the treatment followed the onset of colitis or enteritis. Thus irradiation could have played a part in the development of these conditions in only six of 54 cases.

Case Reports

Case 1. (Serial No. 1043.) A farmer, born in Texas in 1895, had a short episode of diarrhoea, diagnosed as dysentery, while serving in France in 1918. In 1922 he began to have pain and stiffness in the back, shoulders, and hips. In 1947 he stopped work on account of limitation of movement of the spine; ankylosing spondylitis was diagnosed. In 1955 he experienced the onset of bloody diarrhoea, fever, and loss of weight. The stools contained no pathogenic organisms, and in March 1955 he underwent laparotomy and right ileocolectomy. The terminal 28 cm. of ileum were abnormal, the changes becoming progressively more pronounced toward the ileocaecal valve, where they terminated abruptly. Microscopic examination showed acute ulcerative enteritis, hyperplastic lymph follicles, plasma-cell infiltration of the mucosa and submucosa, and oedema and dilatation of lymph channels; no giant-cell systems were seen. *Pathological diagnosis*: regional enteritis. In 1956–7 he had further diarrhoea, with repeated episodes of haemorrhage. Sigmoidoscopy revealed ulcerative proctitis and colitis. X-rays of the spine showed fusion of the sacro-iliac joints, and obliteration of the apophyseal joints of the lumbar and thoracic spine, with severe kyphosis and extensive calcification of the intervertebral ligaments. *Radiological diagnosis*: advanced ankylosing spondylitis. In August 1957 he died from haemorrhage and inanition. At autopsy the remaining part of the small intestine was normal; from the splenic flexure distally the wall of the colon was thickened, and the mucosa showed numerous large linear ulcers consistent with a diagnosis of ulcerative colitis. Fixation of the spine in a position of extreme flexion was noted.

Comment. Ankylosing spondylitis preceded the development of regional enteritis by many years, and probably preceded the development of ulcerative colitis. In two other cases definite regional enteritis was followed by the appearance of radiological changes indicating ulcerative colitis in the descending colon, but sigmoidoscopies were not done. In another case, classified with Case 1 as a 'mixed form' in Table I, granulomatous disease of the colon appeared after ileotransverse colostomy for regional enteritis. Following Marshak and Eliasoph (1958), this case has been regarded as regional enteritis involving the colon.

Case 2. (Serial No. 2011.) A baker, born in 1906 in Colorado, began to have pain and stiffness in both hips in 1943. In 1945 he was discharged from the Army with 'osteoarthritis of both hips' and in 1947 underwent bilateral hip arthroplasties. In 1956 gastrectomy was performed for uncontrollable haemorrhage from a duodenal ulcer. In 1957 he had abdominal colic and melaena, and was noted to have complete fixation of the lumbar, thoracic, and cervical spine, with marked kyphosis; X-rays showed advanced spondylitis, with ankylosis of the sacro-iliac and intervertebral joints. In May 1957 he underwent laparotomy and ileotransverse colostomy. Twelve inches from the ileoceacal valve there was an area of induration, erythema, and oedema of the ileum, extending for several inches. The caecum and large bowel were palpated, and appeared to be normal. *Surgical diagnosis*: regional enteritis. Ileotransverse colostomy was performed. In 1958 the patient had iridocyclitis.

Comment. Although the diagnosis of ankylosing spondylitis was not made until the patient developed symptoms due to regional enteritis, the advanced stage of the disease at that time indicates that it had already existed for many years. In retropect the diagnosis of osteoarthritis of the hips in 1945 was probably erroneous.

Case 3. (Serial No 2030.) A salesman, born in 1930, had iritis in 1948. In 1953 he had bloody diarrhoea while serving abroad; *Entamoeba histolytica* was isolated, and he was treated energetically for amoebic dysentery. Diarrhoea (now unresponsive to amoebicides) recurred in 1954, with fever, loss of weight, and pain in the back. Examination of the stools was negative. Proctoscopy showed a diffusely hyperaemic and granular mucosa, with no ulcers. The barium enema gave findings consistent with a diagnosis of ulcerative colitis. X-rays of the lumbar spine and pelvis showed narrowing and irregularity of both sacro-iliac joints, with subchondral eburnation; the lumbar spine appeared normal. *Diagnosis*: ulcerative colitis with ankylosing spondylitis. In 1955 the patient had pain and swelling of both knees and ankles, the toes of both feet, and the proximal interphalangeal joints of the left hand, and further diarrhoea. Limitation of extension and rotation of the neck was also noted. In 1956 he had acute iridocyclitis.

Comment. This case resembles some of those ascribed to 'Reiter's syndrome'. Iritis, however, preceded the development of amoebic dysentery by five years. This is the best documented of three instances (see also Case 1) in which 'dysentery' had been diagnosed at an early stage. It also illustrates the occasional development of symmetrical peripheral joint disease in such cases (Table III).

Case 4. (Serial No. 1936.) A plumber, born in Vermont in 1912, began in November 1944 to have back pain, pain round the chest on breathing deeply or sneezing, and pain in the right hip. He was noted to have flattening of the normal lumbar curvature, thoracic scoliosis, limitation of movement of the dorsal and lumbar spine, and of rotation of the right hip, and tenderness over the sacrum. X-rays of the lumbar spine and pelvis showed sclerosis of the margins of both sacro-iliac joints, with ossification of the ligaments between T12 and L1 and between L3 and L4. He was discharged from the Army with a diagnosis of ankylosing spondylitis. In June 1945, while travelling home on the day following his discharge, he experienced the sudden onset of bloody diarrhoea. He was admitted to a Veterans Administration hospital. The report on the barium enema stated 'The walls of the transverse and descending colon appear rigid and moth eaten, and have lost the normal mucosal pattern', and on sigmoidoscopy 'A granular mucosa with a few small haemorrhagic areas and one small irregular ulcer'. *Diagnosis*: ulcerative colitis. A further exacerbation of ulcerative colitis occurred in 1951. In 1956 total colectomy was performed, with excision of the rectum. The pathological findings were typical of chronic ulcerative colitis.

Comment. Ulcerative colitis followed closely on the onset of ankylosing spondylitis.

Case 5. (Serial No. 2019.) The patient was born in Wisconsin in 1935. In 1946 he was sent to a sanatorium for 'tuberculosis of the bowel', characterized by bloody diarrhoea and loss of weight. Tubercle bacilli were reported in the stool, although there was no evidence of pulmonary disease. He recovered without specific therapy. In 1956 he experienced the onset of pain in the left hip while marching, and bloody diarrhoea. Sigmoidoscopy showed a 'friable, red, contracted bowel'. On the barium enema X-rays haustrations appear to be absent; marginal serrations are evident, and there is an area of constriction in the sigmoid. X-rays of lumbar, spine and pelvis show sclerosis along the margins of both sacro-iliac joints; the joint space of the left hip is narrowed. The lumbar spine appears normal. *Diagnosis*: ulcerative colitis and ankylosing spondylitis. In 1957 total colectomy was performed. *Pathological diagnosis*: advanced ulcerative colitis.

Comment. If it is assumed, as seems reasonable in retrospect, that this patient's early episode of diarrhoea was mistakenly diagnosed as due to tuberculosis, this case illustrates the more unusual sequence of events, namely the development of spondylitis after ulcerative colitis.

Case 6. (Serial No. 1045.) A negro truck driver, born in 1932 in Georgia, had acute intestinal obstruction in 1952. Laparotomy and ileocolostomy were performed with excision of the caecum and 70 cm. of thickened, inflamed, and oedematous ileum. On histological examination the mucosa of the ileum was diffusely infiltrated by lymphocytes, plasma cells, and polymorphs. The submucosa was markedly thickened by oedema and proliferating connective tissue. The musculature was hypertrophied, and the peritoneum thickened and inflamed. *Diagnosis*: regional enteritis. In 1955 the patient began to have backache and pain in both hips. On X-rays of the lumbar spine and pelvis the sacro-iliac joints are irregular and widened, and show subchondral sclerosis. The apophyseal joints of the lumbar spine show similar changes. *Diagnosis*: early ankylosing spondylitis.

Comment. A rare instance in which regional enteritis appeared before ankylosing spondylitis.

Review of Published Reports

Ankylosing spondylitis has not generally been recognized as a condition which is associated with ulcerative colitis or regional enteritis. Monaghan (1944), Palmer (1959), and Texter (1957) in his detailed review, mentioned arthritis as a complication of ulcerative colitis, but did not indicate specifically which joints were involved. Sloan, Bargen, and Gage (1950) were scarcely more definite in their statement that 155 of their patients with ulcerative colitis had 'infectious arthritis, rheumatoid arthritis or spondylitis'. Hightower, Broders, Haines, McKenney, and Sommer (1958) mentioned 'rheumatoid arthritis' as one of the complications found in a series of 220 cases. In the British literature, ankylosing spondylitis was not mentioned in the extensive series of Hardy and Bulmer (1933), Rice-Oxley and Truelove (1950), or Cullinan and MacDougall (1957). Before the publication of Fernandez-Herlithy's series (1959), in which he described 28 instances of ankylosing spondylitis in 555 patients with ulcerative colitis, positive reports of the association were scanty, and there was little to indicate that a factor other than chance was operating. Flood, Lepore, Hiatt, and Karush (1956) had mentioned that two of their 148 patients suffered from Marie-Strumpell arthritis. Bacon (1958) gave photographs of the sacro-iliac joints and of a surgical specimen of the colon from a patient with advanced ankylosing spondylitis and ulcerative colitis. McEwen, Ziff, Carmel, Ditata, and Tanner (1958), in an investigation of the relation of rheumatoid arthritis or its 'so-called variants', reported seven further instances of the association of 'characteristic ankylosing spondylitis' and ulcerative colitis. Bywaters and Ansell (1958) mentioned involvment of the sacro-iliac joints, identical with that seen in ankylosing spondylitis, in six of 37 patients with ulcerative colitis and various forms of arthritis. There are also a few reports of coexisting ulcerative colitis in cases of ankylosing spondylitis. Romanus (1953) mentioned three cases, of which one was doubtful. Steinberg and Storey (1957) described four cases of ulcerative colitis in 399 instances of ankylosing spondylitis, and felt that the frequency of 1 per cent. was greater than might have been expected by chance. Wilkinson and Bywaters (1958) found four instances of ulcerative colitis in a series of 242 cases of ankylosing spondylitis. Reported instances of regional enteritis associated with ankylosing spondylitis are much less common. Van Patter, Bargen, Dockerty, Feldman, Mayo, and Waugh (1954) found 27 cases of 'polyarthritis of the rheumatoid type' in 600 cases, and noted that the spinal column was occasionally involved. Crohn and Yarnis (1958) found arthritis, usually of the large joints, in 17 of their 542 cases, and mentioned that the cervical spine was affected in one case. Steinberg and Storey (1957) described a case of ankylosing spondylitis and regional enteritis, and a further instance in which both ulcerative colitis and regional enteritis were present. Wilkinson and Bywaters (1958) found regional enteritis in one of their cases of ankylosing

spondylitis. Prior to the present report there were thus 54 published instances of ankylosing spondylitis in association with ulcerative colitis, and two with regional enteritis, and one instance in which all three conditions occurred in the same patient.

Discussion

Although 54 cases of ankylosing spondylitis associated with either ulcerative colitis or regional enteritis, or both, are recorded in this paper, only 42 can be used in the formal comparison of frequencies which is made in Table I. The other 12 cases had been classified as rheumatoid arthritis, and their nature became known only after a detailed study of their clinical records and X-rays. No comparable survey was made of rheumatoid arthritis in association with the other diagnoses. The addition of the 12 cases raises the frequency of the association of ankylosing spondylitis with regional enteritis to 3·0 per cent., and with ulcerative colitis to 2·6 per cent. The defects of a retrospective study such as this make it reasonable to suppose that additional cases were missed. Table I shows that the diagnosis 'ankylosing spondylitis' was made in persons with regional enteritis or ulcerative colitis 20 times as often as in a 25 per cent. systematic sample of all patients admitted to the general medical or surgical beds of Veterans Administration hospitals. Although this difference is well beyond the limits of sampling error, it might be due to other differences between the groups. For this reason information was collected from cases of two chronic diseases with age distributions similar to those of regional enteritis and ulcerative colitis. In 675 admissions for Hodgkin's disease, ankylosing spondylitis was not encountered; and only two instances of the disease were found in 813 cases of multiple sclerosis. It can be argued that ankylosing spondylitis was looked for more thoroughly in ulcerative colitis and regional enteritis than in Hodgkin's disease and multiple sclerosis, because of their known association with other forms of inflammatory joint disease. This argument is answered by the magnitude of the difference, and also by the evidence that in 12 of 31 cases of ulcerative colitis, and 14 of 22 cases of regional enteritis, spondylitis had been diagnosed before the abdominal condition. Another possibility is that the treatment of the prior condition brought on the other. As far as deep irradiation therapy is concerned, it has already been shown that it preceded the development of ulcerative colitis or regional enteritis in only six cases. There is no reason to suppose that any other type of treatment could bear on the association.

If the reality of the association is accepted, it remains to speculate on its nature. Clearly ankylosing spondylitis cannot be regarded as a complication either of ulcerative colitis or regional enteritis, for symptons of it came first in the majority of cases; this removes any likelihood that the sacro-iliitis is caused by sepsis spread by way of the pelvic lymphatics or veins, as suggested by Romanus (1953) in cases of ulcerative colitis associated with prostatitis. Although a number of different types of association between diseases are possible, an obvious one is that both may be manifestations of one general disorder.

From this standpoint it is of interest that in one instance (Case 3) uveitis preceded both spondylitis and ulcerative colitis.

The common association, at similar frequencies, of ankylosing spondylitis with both ulcerative colitis and regional enteritis is a connecting link between the two latter disorders. Other links are the occurrence of both in members of the same family (Houghton and Naish, 1958) and in the same person (Marshak and Eliasoph, 1958), the sharing of such associated disorders as uveitis, erythema nodosum, and polyarthritis, and the existence of the pathological no-man's-land of enterocolitis (Lumb, 1951) between typical instances of the two conditions.

In conclusion it is necessary to mention 'Reiter's syndrome'. This term is used in so many different senses (Buchan, 1955) that it has become a semantic obstacle. Marche (1950) has used the term to include cases of bilateral sacro-iliac disease following bacillary dysentery. According to Oates and Young (1959) sacro-iliac disease may be associated with urethritis under this heading. In the present series dysentery was recorded as having preceded the illness definitely in one instance, and possibly in two others. A previous attack of gonorrhea was recorded in three cases, which in a population of ex-servicemen is not surprising. Prostatis was not encountered.

Dr. W. E. Chamberlain kindly gave his opinion on the X-rays in doubtful cases. I also acknowledge gratefully the helpful critcism of Dr. Martin Cummings and Dr. Clifford A. Bachrach. The investigation was done during the author's tenure of a Radcliffe Travelling Fellowship of University College, Oxford.

Summary

1. Thirty-one cases of ulcerative colitis, 22 cases of regional enteritis, and one instance of both conditions occurring consecutively in the same patient, are reported in association with ankylosing spondylitis. These cases represented 3·0 per cent. of all male patients with regional enteritis discharged from Veterans Administration hospitals during the years 1953 to 1957, and 2·6 per cent. of all male patients discharged with ulcerative colitis during 1956 and 1957.

2. The diagnosis 'ankylosing spondylitis' was found to have been made in patients with ulcerative colitis and regional enteritis about 20 times as frequently as in a sample of all general medical and surgical admissions, or in patients with multiple sclerosis of Hodgkin's disease.

3. In the majority of cases the onset of ankylosing spondylitis preceded the onset of ulcerative colitis or regional enteritis.

4. A study of published reports revealed 54 instances of ankylosing spondylitis and ulcerative colitis, two of ankylosing spondylitis and regional enteritis, and one of all three conditions in the same patient.

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LUNG PURPURA WITH NEPHRITIS[1]

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With Plates 39 to 41

The association of glomerulonephritis with haemorrhage into the skin and mucous membranes is not infrequent, and is generally attributed to a common allergic cause. A similar association between nephritis and pulmonary haemorrhage, however, is less well recognized, although examples have occasionally been recorded. Osler (1895), in his description of the visceral complications of erythema exudativum multiforme, noted the frequency of nephritis, and mentioned haemoptysis as occurring in two patients, but in neither was bleeding from the lungs a formidable symptom. Goodpasture (1919), studying the pulmonary complications of influenza after the First World War, described the necropsy findings in a patient with gross haemorrhage into the lungs and proliferative glomerulonephritis, and made the comment that the appearance was unusual. Parkin, Rusted, Burchell, and Edwards (1955), under the title 'Haemorrhagic and interstitial pneumonitis with nephritis', recorded seven patients in whom haemoptysis was an early and important symptom; in four of these the clinical and histological findings resembled those of polyarteritis nodosa. Single examples of the association have been recorded at Hammersmith Hospital (1954) and by Scadding (1958). Stanton and Tange (1958) collected nine examples of pulmonary haemorrhage with glomerulonephritis, of which three presented the features of polyarteritis nodosa. Heptinstall and Salmon (1959) have published three additional cases, of which two are certainly examples of the syndrome we are about to describe. Our purpose is to place on record five examples of nephritis with frank haemoptysis as a presenting and prominent feature, to give reasons for believing that this syndrome merits separate clinical classification, and to discuss the relationship between it and other disorders to which it is in some respects allied.

Case Reports

Serial changes in blood-pressure and laboratory data are summarized in the Table (page 503).

Case 1. P. H., a naval engineer apprentice, aged 17, was perfectly well until October 1956, when he complained of haemoptysis over the course of a week.

[1] Received August 22, 1959.

No other symptoms appeared until February 1957, when haemoptysis recurred and he was admitted to a naval hospital for investigation. Physical examination, chest X-rays, and erythrocyte sedimentation rate were normal. Haemoglobin was 78 per cent. Clotting and bleeding times were normal. He continued to expectorate blood-stained sputum for the next two months. On 6.4.57 he was found for the first time to be passing albumin and blood in the urine. Haemoglobin was 60 per cent., red cells 3,300,000 per cu.mm., blood urea 141 mg. per 100 ml., erythrocyte sedimentation rate (Westergren) 70 mm. in one hour, and plasma proteins 6·0 g. per 100 ml. (albumin 3·2 g., globulin 2·8 g.). From this time onwards the illness progressed rapidly. The volume of urine passed was small, and the blood urea increased. On 15.4.57 he was transferred to The London Hospital.

On examination he was pale and drowsy, with puffiness of the face and slight twitching of the facial muscles. The blood-pressure was normal; blood urea was 433 mg. per 100 ml., serum potassium 10·8 m-equiv. per litre, and haemoglobin 45 per cent. During the first 12 hours in hospital the patient passed no urine. In the second 12 hours he passed 210 ml., and none for the next two days. He was vomiting. The urine contained albumin, red cells, and granular casts. During these three days he received 40 per cent. glucose with insulin by catheter into the femoral vein, and cation exchange resin by rectum; the blood-urea level remained stationary, and the serum-potassium decreased slightly. He was transferred to Hammersmith Hospital for consideration of artificial haemodialysis, but this was not carried out. The blood urea increased to 680 mg. per 100 ml. A grave worsening of the anaemia necessitated blood transfusion. On 23.4.57 he died after a large haemoptysis.

Necropsy. The abnormal changes were virtually confined to the lungs and kidneys.

Lungs. The visceral pleurae presented a mottled red and red-purple haemorrhagic appearance, and on section large amounts of oedema fluid flowed freely from the cut surface. The lung parenchyma showed a similar mottled appearance. Microscopically the most striking feature was the presence of marked but irregular alveolar haemorrhages, which filled the alveolar sacs and many of the respiratory bronchioles (Plate 39, Fig. 1.). The bronchi and larger bronchioles were free of blood. In some fields many pigmented macrophages were seen, which were shown to contain haemosiderin. The alveolar walls were thickened, and contained neutrophile leucocytes and a moderate amount of fibrin, but appeared intact.

Kidneys. Both kidneys were increased in size, and were soft and flabby. The capsules stripped easily, leaving a smooth surface, yellow-brown in colour, with numerous petechial haemorrhages. Microscopically there was a diffuse glomerulonephritis. All the glomeruli showed a variety of lesions, including hyaline necrosis of the tufts, proliferative glomerulitis, haemorrhage into Bowman's space, epithelial crescent formation, capsular adhesions, and pericapsulitis (Plate 39, Fig. 2.). Tubules showed focal atrophy, with slight dilatation, occasional hyaline-droplet degeneration, and numerous blood casts. There was diffuse interstitial inflammation, with early focal fibrosis. Occasional necrosis of glomerular arterioles (not fibrinoid), with intense periarteriolitis, was seen.

Case 2. T. B., an able-bodied seaman aged 20, was well until August 1957 when, on return from service in the Far East, he experienced tiredness after an an attack of 'Asian' influenza complicated by sore throat and a rash. No other symptoms appeared until December 1957, when blood-spitting started and

Serial Data of the Five Cases

	Case 1 *Male, aged 17*			*Case 2* *Male, aged 20*			*Case 3* *Male, aged 22*			*Case 4* *Male, aged 21*			*Case 5* *Male, aged 19*		
Months after first haemoptysis	4½	5½	6	2	5	8	1	2½	3½	8½	9	11	5	7	9
Blood-pressure (mm. Hg)	..	..	120/65	110/85	150/100	180/110	110/70	130/80	130/80	150/90	..	140/80	130/75	140/98	170/115
Haemoglobin % (Haldane)	78	74	60	67	71	21	50	54	30	60	86	89	72	60	27
White blood-cells (per cu. mm.)	10,200	9,200	15,300	13,400	14,700	..	7,050	..	12,800	4,700	5,000	5,200	11,200	..	..
Polymorphs %	66	64	79	66	65	..	71	..	98	55	53	72	57	..	..
Eosinophils %	4	2	0	2	1	..	1	..	0	0	1	1	3	..	..
Erythrocyte sedimentation rate (mm/hour) (Westergren)	4	33	70	25	50	..	10	..	108	28	5	7	4	32	..
Blood urea (mg./100 ml.)	..	..	141 to 433	33	48	294	..	112	400	..	..	36	..	180	170
Plasma proteins (g./100 ml.)															
Total	..	..	6·0	7·2	5·6	5·0	5·9	..	7·1	..	..	..	..	..	..
Albumin	..	..	3·2	4·5	3·0	3·0	4·0	..	3·8	..	..	..	..	..	..
Globulin	..	..	2·8	2·7	2·6	2·0	1·9	..	3·3	..	..	..	..	..	..
Total duration	6 months (Died)			12 months (Died)			3½ months (Died)			3 years (Still alive)			9 months (Died)		

continued at intervals. He became breathless. On 8.2.58 he was admitted to a naval hospital. On admission he looked ill and anaemic. Red blood-cells numbered 3,400,000 per cu. mm. X-rays of the chest showed diffuse, rather coarse, opacities in the central and lower portions of both lung fields. The urine contained albumin, excess of red cells, and granular casts. He was admitted to the London Hospital on 23.2.58.

On examination he had no fever; the pulse rate was 80 to 90, blood-pressure 135/95, haemoglobin 67 per cent., and reticulocytes 0·8 per cent.; the Coombs teat was negative, and the erythrocyte sedimentation rate (Westergren) 25 mm. in one hour. The urine showed a very heavy precipitate of albumin; red blood-cells and granular casts were constantly present. Serum electrolytes were normal; blood urea was 33 mm. per 100 ml., and creatinine clearance was 44 ml. per minute. The sputum was blood-stained, and revealed many macrophages containing iron pigment. Chest X-rays were now normal. Twelve days after his admission prednisone, 10 mg. thrice daily, was given for one week, followed by 20 mg. thrice daily. Albuminuria, haematuria, and haemoptysis were unaffected by this treatment, but the blood-urea level rose in three weeks to 159 mg. per 100 ml. The dose was therefore reduced to 5 mg. thrice daily for seven days, and the blood urea at once decreased to 41 mg. per 100 ml. He was given a low-protein, low-salt diet, and on one occasion, when the haemoglobin had dropped to 40 per cent., he received a transfusion of packed cells, with temporary improvement. During the next five months the illness followed the course of a progressive type 1 nephritis. The blood-pressure rose to 180/110, and oedema appeared. Moderate papilloedema was noted, but no haemorrhages or exudates were seen in the fundi. The volume of urine fell, and the blood urea increased to 294 mg. per 100 ml. Haemoptysis continued at intervals, and transfusions of packed cells were given. He died on August 12, 1958.

Renal biopsy was carried out on three occasions during the last six months of the illness, and the following is a summary of the findings.

First biopsy (4.3.58). Twelve glomeruli were seen in the section, of which only three showed definite abnormality. Focal cellular proliferation, irregular thickening of the basement membrane, adhesions to Bowman's capsule, and localized epithelial proliferation, were present in these glomeruli (Plate 40, Fig. 3); there were a few red blood-cells in the capsular spaces. Many tubules contained red cells or red-cell casts. There was slight cellular increase in the interstitial tissue. No vascular lesions were seen.

Second biopsy (15.4.58). Twenty-two glomeruli were present, and all showed severe disorganization (Plate 40, Fig. 4), with partial or complete hyaline necrosis of tufts, capsular adhesions, and epithelial crescent formation. The tubules showed diffuse atrophy and focal dilatation, with occasional blood casts in the lumen. There was diffuse increase in interstitial tissue, and periglomerular fibrosis. Some arterioles showed (non-fibrinoid) necrosis and marked periarteriolar inflammation. This picture corresponds to a severe, rapidly progressive type 1 nephritis resembling that described in Case 1, and is in marked contrast to the mild focal nephritis revealed by the first biopsy.

Third biopsy (10.5.58). Seventeen glomeruli were present. All were abnormal, and showed more advanced glomerular hyalinization than previously. The epithelial crescents had undergone organization, and interstitial inflammation was more severe.

Necropsy. The important changes were confined to the lungs and kidneys.

Lungs. Macroscopically the lungs were bulky and contained blood, and in all respects resembled those of the preceding case. Microscopically the bronchial

tree was normal; there was no increase in the lymphoid tissue, but the lymphatics were slightly dilated. The pulmonary arteries and veins were normal. In the alveoli and respiratory bronchioles the capillaries were moderately congested. The elastic tissue and reticulin in the alveolar walls were intact (Plate 40, Fig. 5). Oedema fluid was present but not excessive, and little fibrin or evidence of organization was seen. Red cells indicative of recent haemorrhage were visible in many of the alveoli, together with macrophages containing haemosiderin. The interstitial tissue was spared. Iron-containing macrophages were present in the hilar lymph-nodes. No arteritis was seen in any of the vessels. The picture was essentially that of past and recent intra-alveolar haemorrhage, and no clear evidence of necrosis of the alveoli could be detected.

Kidneys. The appearance confirmed the second and third biopsy findings of an intense diffuse glomerulonephritis undergoing organization. Occasional fibrinoid glomerular and arteriolar necroses were seen, and hyaline-droplet degeneration of the tubular epithelium was present.

Case 3. P. B., a man aged 22, had had no serious illness until October 1957, when he had left frontal sinusitis with extradural abscess. *Staph. aureus* was grown from the pus, and he received penicillin, tetracycline, and novobiocin, each for five days. He had two operations. He recovered and returned to work, but never felt completely well, and expectorated a little yellow sputum each day. In June 1958 he coughed up blood on several occasions, and was investigated at a chest clinic. Haemoglobin was 88 per cent., and the blood-pressure 130/90. X-rays of the chest showed diffuse changes in the lungs (Plate 41, Figs. 8 and 9). On 12.7.58 he was admitted to a local hospital, where it was noted that his general condition was good, blood-pressure 110/60, haemoglobin 50 per cent., and the erythrocyte sedimentation rate (Westergren) 10 mm. in one hour. The urine contained albumin, many red cells, and granular casts. His condition deteriorated owing to the development of uraemia. He was transferred to The London Hospital under the care of Dr. J. T. Wright on 13.9.58.

At the time of his admission the daily volume of urine was less than 250 ml., the blood-pressure was 130/80, blood urea 400 mg. per 100 ml., plasma sodium and chloride normal, plasma bicarbonate 10 m-equiv. per litre, and plasma potassium 10 m-equiv. per litre. The erythrocyte sedimentation rate (Westergren) was 108 mm. in one hour, plasma albumin 3·8 g. and globulin 3·3 g. per 100 ml., and haemoglobin 39 per cent. In response to 50 per cent. glucose given intravenously, insulin, and cation exchange resin, the level of blood potassium fell and the plasma bicarbonate increased. There was, however, little improvement in the patient's clinical condition. Prednisone, which had been given for three weeks, was without influence on the course of the disease. His sputum was heavily blood-stained; he became confused and restless, and vomiting and hiccup were prominent symptoms. Anuria developed, the blood-urea level rose to 660 mg. per 100 ml., and the patient died on 22.9.58.

Necropsy. Apart from the alimentary tract, in which a few petechial haemorrhages were noted, the changes were again confined to the lungs and kidneys.

Lungs. The pleurae were smooth, with purple-yellow mottling over the surface. The lungs were diffusely oedematous, and the cut surface was dotted with pale-pink and dark-brown areas of haemorrhage. The lymph-nodes at the lung root were soft and pigmented. Microscopically, evidence of recent haemorrhage was seen in many of the alveoli, with iron-laden macrophages (Plate 41, Fig. 6), some in clumps and others more diffusely scattered in and around the

areas of haemorrhage. The alveolar walls were intact, contained no haemosiderin, and only rarely showed thickening of the reticular structure. The pulmonary and bronchial vessels of all calibres were normal, and no arteritis was found. Macrophages containing haemosiderin were seen in the hilar lymph-nodes. As in the preceding examples, the changes were limited to those of haemorrhage into the alveoli.

The kidneys were not contracted. Microscopically no normal glomeruli were seen. There was a severe haemorrhagic glomerulitis, with endothelial proliferation of the tufts, infiltration with polymorphonuclear leucocytes, large epithelial crescents, and severe acute and chronic periglomerular inflammation (Plate 41, Fig. 7). Tubules showed diffuse, severe atrophy, hyaline-droplet and fibrinoid degeneration of the epithelium, blood, leucocytes, and epithelial and fibrin casts. Fibrinoid glomerular and arteriolar necroses were seen; one interlobular artery had undergone necrosis of its wall, with disappearance of the elastica interna and irregular intimal proliferation (endarteritis).

Case 4. R. T., a naval cook aged 21, coughed up blood in October 1956, when training at the 100-foot tank for submarine free ascent. Physical examination and chest X-rays were negative. During the next six months he expectorated blood-stained sputum at intervals. He also noticed breathlessness on exertion, and a loss of 7 lb. in weight. On 7.5.57 he was admitted to a naval hospital. He was pale, and looked ill. The blood-pressure was 150/90. Moist sounds were heard throughout both lungs. X-rays of the chest showed symmetrical soft stippling in both lungs. The haemoglobin was 60 per cent.; the erythrocyte sedimentation rate (Westergren) was 28 mm. in one hour. During the next three weeks the patient improved, and the X-ray changes cleared completely. Haemoptysis then recurred, and for the first time the urine was found to contain albumin and red cells.

On 6.7.57 he was transferred to The London Hospital. On examination no abnormal signs were detected. The sputum showed macrophages laden with iron pigment. X-rays of the chest were normal. The blood Wassermann reaction was negative, and the serum electrolytes within the normal range. The tourniquet test for capillary fragility was positive, the Race–Coombs test was negative, and the antistreptolysin O titre 192 units per ml. The urine showed a granular deposit of albumin, blood and granular casts being present. Blood urea was 36 mg. per 100 ml., and the tests of renal function were normal. Prednisone, 10 mg. four times daily, was given for five days, and then 10 mg. thrice daily. The patient's general condition remained satisfactory, and haemoptyses diminished. He was invalided from the Navy, and in June 1959, two and a half years after the onset of symptoms, was well and working. He had occasional slight haemoptysis, but the urine was free of albumin, red cells, and casts. The haemoglobin was 106 per cent., the erythrocyte sedimentation rate (Westergren) was 4 mm. in one hour, and X-rays of the chest were normal. He had continued to take 5 mg. prednisone daily until April 1959, when it was discontinued.

Case 5. A. O., aged 19, a stoker-mechanic, was admitted to a naval hospital in January 1949 with the complaint of blood-spitting. There were no other symptoms, and the past history contained no relevant illness. Physical examination was negative, X-rays of the chest were normal, and no acid-fast bacilli were found on examination of six specimens of sputum. At bronchoscopy a dilated blood-vessel was observed in the right main bronchus, and was taken

to be the probable source of the haemorrhage. As no further bleeding occurred, he was sent on sick leave.

During the next four months flecks of blood were seen in the phlegm from time to time, and breathlessness on exertion was noticed. He was admitted to another naval hospital for further investigation. There were no clinical signs in the lungs or elsewhere. The blood-pressure was 120/70. Chest X-rays were normal, and bronchoscopy revealed no abnormality. Red blood-cells numbered 3,060,000 per cu.mm. and the haemoglobin was 50 per cent. The urine contained albumin and granular casts; the specific gravity was 1,010; culture was sterile. The blood urea was 100 mg. per 100 ml., and urea clearance 10·5 per cent. Bleeding time was two minutes, and clotting time 10 minutes 36 seconds. Cystoscopy, and intravenous and retrograde pyelography, were normal. For the next few weeks his condition underwent little change. Anaemia persisted, and the albuminuria increased after an attack of acute tonsillitis. Fever up to 100° F was recorded at intervals. He complained occasionally of frontal headaches, and vomited on two or three occasions. The blood-pressure did not rise, and there was no oedema. Blood-urea readings ranged from 114 mg. to 174 mg. per 100 ml. In September 1949 he was invalided from the Service with a diagnosis of chronic nephritis, and transferred to his home. He was admitted to hospital on 4.10.49. Haemoptysis had recurred severely four days before his admission, and oedema had developed. There were signs of pulmonary congestion. The blood-pressure was 170/115. The urine contained albumin, many red cells, and scanty pus cells. The blood urea was 170 mg. per 100 ml., and haemoglobin 27 per cent. His condition rapidly deteriorated, and he died three days later, on 7.10.49.

Necropsy. There was marked oedema of the subcutaneous tissues. The lungs were congested and oedematous. The kidneys were enlarged and firm, and the capsules stripped easily. Microscopically there was severe disorganization of the renal pattern, but the glomeruli were not reduced in number. A diffuse glomerulitis, with epithelial crescents, was the predominant finding. No vascular lesions were seen. The tubules were not dilated. The appearance was that of a rapidly progressive type 1 nephritis. Unfortunately details of the microscopy of the lungs are not available.

Summary of Clinical Features

The illness in these five patients displayed a similar pattern. They were all male, the youngest being 17 and the oldest 22 years of age. Four of the five died. The total duration of the illness in those who died ranged from three and a half to nine months. Haemoptysis was the first, and for a time the only, symptom. The extent and form of the bleeding showed much variation. At first attacks of slight or moderate haemorrhage were punctuated by intervals of freedom; later a more regular and persistent staining of the sputum was observed. In all cases, at some stage, considerable loss of blood took place, and it was on such occasions that clinical signs in the lungs were found and changes in the X-ray seen. These changes consisted of diffuse, fine or coarse, often confluent opacities in one or both lungs, and proved transitory if bleeding ceased or lessened (Plate 41, Figs. 8 and 9). Haemoptysis was eventually accompanied by anaemia out of proportion to the amount of blood visibly lost, the haemoglobin falling to 50 per cent. or less. Examination of the sputum after haemorrhage disclosed

macrophages loaded with iron pigment ('siderophores') whenever these were looked for. Shortly after the onset breathlessness on exertion, lassitude, and loss of weight became noticeable, but were rarely obtrusive. It will at once be apparent that during this stage of the disease the features were completely in accordance with those of idiopathic pulmonary haemosiderosis, and indeed this diagnosis would inevitably have been made but for the appearance of a second and more serious phase of the disorder.

This second phase was ushered in by the discovery, often on routine examination, of abnormal constituents in the urine. The interval that elapsed between the first complaint of haemoptysis and the recognition of albumin, red blood-cells, and cellular casts in the urine, varied from five weeks in Case 3 to eight months in Case 4. In the early stages the urinary changes were unaccompanied by symptoms, fever was rarely observed, the blood-pressure was not raised, there were no changes in the ocular fundi, the erythrocyte sedimentation rate was normal or only slightly elevated, and the serum electrolytes were unaltered. Yet the nephritis was in most cases steadily and rapidly progressive, and was the cause of death in each of the four fatal cases. In Case 1 only six weeks passed between the detection of albumin in the urine and death; in Case 5, in which this interval was the longest, five months elapsed. Sooner or later, in all but one patient, renal failure set in, the blood urea increasing to over 400 mg. per 100 ml. in three cases. Changes in the serum electrolytes included elevation of the serum-potassium level as a characteristic feature. Hypertension became established, papilloedema was observed in one patient, and the erythrocyte sedimentation rate rose in three. Drowsiness, vomiting, and tremor were frequently seen. The urine output gradually diminished, and oedema of the face and dependent parts appeared. Death occurred from uraemia, with anuria, and severe haemorrhage from the lungs was the final event in one patient.

Discussion

A study of these clinical features, and a comparison with other reported cases, indicate that this syndrome is a clinical entity with a remarkably consistent pattern and course. The repeated attacks of haemoptysis, with no clinical or radiological evidence of progressive lung disease, contrast strikingly with the severity of the renal lesion and the rapid development of renal insufficiency. The early appearance of haemoptysis and the late development of renal failure distinguish this syndrome from acute nephritis in which haemoptysis occurs as a result of uraemia or left ventricular failure. Acute nephritis, focal or diffuse, may follow an attack of pneumonia, but there was in our cases no clinical or radiological evidence of consolidation or bacterial infection of the lungs.

The pulmonary lesion. The term 'necrotising alveolitis' was used by Parkin, Rusted, Burchell, and Edwards (1955) in describing cases similar to those reported above. The absence of necrotizing changes in the material we have studied indicates that alveolar necrosis is not an essential feature of the pul-

monary lesion. It is possible that the thickening and degeneration of the alveolar walls may be the result of the recurrent haemorrhage and not its cause, or may even be an independent finding. In view of this uncertainty we prefer to use the term 'lung purpura' as being descriptive yet non-committal. From the clinical point of view the similarity, in the early stages, between this disease and idiopathic pulmonary haemosiderosis has already been referred to. The length of illness in our patients was shorter than is usual in idiopathic pulmonary haemosiderosis; on microscopy red cells and iron-containing macrophages were confined to the alveoli and absent from the interstitial tissue, and there was no impregnation of the elastic tissue with iron. These differences can probably be ascribed to the fact that the renal lesion brought the illness to a premature conclusion. Only rarely is idiopathic pulmonary haemosiderosis accompanied by renal disease. Heptinstall and Salmon (1959) searched the literature for information on this point, and found that of 69 recorded examples of idiopathic pulmonary haemosiderosis only five were complicated by renal lesions. It is interesting to note that all these instances were in children under the age of 14 years. Fuller reference is made to this association later. X-ray changes are seen only at the time of a large haemorrhage. They are mainly concentrated in the middle and lower portion of the lungs, and may be bilateral. The rapidity with which they disappear after haemoptysis has ceased is more consistent with the absorption of blood than with the resolution of inflammatory or necrotic changes.

The renal lesion. The opportunity to make biopsy and necropsy studies in our cases has enabled us to define and follow the development of the renal lesion. In the final stages, illustrated by the necropsy appearances of our fatal cases, the histological pattern is remarkably uniform. It consists of an intense diffuse glomerulonephritis, corresponding to the rapidly progressive type 1 nephritis of Ellis's (1942) classification. The glomeruli are grossly disorganized, epithelial crescent formation is present, periglomerular inflammation is common, and there may be fibrinoid necrosis. The tubules may show hyaline-droplet degeneration and contain altered blood. Acute necrosis of the arterioles and interlobular arteries was seen, but such lesions are sparse; there was no evidence of polyarteritis involving the larger arteries. The early stages of the development of the lesion were shown by serial biopsy studies in Case 2. The early change was a focal glomerulonephritis, in which occasional glomeruli showed focal necrosis and capsular adhesions similar to those observed in other types of focal nephritis associated with haematuria. Interstitial, tubular, and vascular changes were minimal at this stage. In this patient the transformation from a mild focal nephritis into an intense diffuse glomerulonephritis took place between the first and second biopsies, that is within the space of five weeks (Plate 40, Figs. 3 and 4). From a study of the sections it is clear that they represent two distinct episodes of renal damage. This transition from focal to diffuse nephritis had its clinical counterpart, for oedema, hypertension, and renal failure were absent early in the illness, but appeared rapidly towards the end. A similar sequence may have occurred in Case 5. These findings may clarify the relationship between the cases we are describing and idiopathic pulmonary

haemosiderosis. The renal lesion occasionally found in idiopathic pulmonary haemosiderosis is usually recorded as a focal nephritis. Our observation that focal nephritis and diffuse nephritis may occur in sequence in the same patient strongly suggests that idiopathic pulmonary haemosiderosis and lung purpura with nephritis differ only in the presence and severity of the renal lesion.

There remains for consideration the broader question of the relationship of this syndrome to other conditions. Glomerulonephritis is frequently seen in the Schönlein–Henoch syndrome, and renal failure is the commonest cause of death in this disease. For example, Gairdner (1948) found nephritis in 11 of the 12 children with this form of purpura. It seems reasonable to conclude that the syndrome we have described is the same kind of disorder as the Schönlein–Henoch syndrome, the lungs being involved in place of the skin, joints, and alimentary tract. If this is so, it appears likely that idiopathic pulmonary haemosiderosis is a purpuric state with a similar pathogenesis, remarkable in that the lungs are almost invariably the only organs affected. There is no evidence pointing to the primary cause. Infection with the haemolytic streptococcus has been invoked to explain the Schönlein–Henoch syndrome; the only evidence of infection in our cases was a staphylococcal sinusitis preceding the onset in Case 3, and an attack of follicular tonsillitis in the course of the illness in Case 5.

Lung purpura with nephritis bears some resemblance to other allergic or collagen disorders. Other cases, in many respects similar to our own, have been reported in which generalized vascular changes of polyarteritis occurred (Parkin, Rusted, Burchell, and Edwards, 1955; Stanton and Tange, 1958), so that a hard-and-fast line of division between the two conditions is difficult to draw. Acute glomerulonephritis may be a complication, or even a presenting feature, of polyarteritis nodosa (Davson, Ball, and Platt, 1948) and is usually focal in distribution. Haemorrhage from the respiratory tract may take place in Wegener's granulomatosis, a condition allied to polyarteritis nodosa, in which renal lesions are common and severe. There are important differences, however, between Wegener's granulomatosis and the condition we are describing. Nevertheless, it is apparent that the 'lung purpura–nephritis syndrome' can occur in the absence of any of the features commonly associated with polyarteritis, such as persistent fever, eosinophilia, raised erythrocyte sedimentation rate, leucocytosis, and polyneuritis. In our cases arteritis was not seen in any of the larger vessels, and was only occasionally observed in the smaller vessels of the kidney. The rapidly developing anaemia which was found in three of our patients is often a feature of progressive collagen disease. It was not adequately explained by loss of blood, and was refractory to treatment. There was no evidence that the anaemia was haemolytic. The failure of response to steroid therapy is typical of other forms of collagen disease with renal involvement. In our series the two patients who showed no response to steroid therapy had renal impairment when treatment was begun; on the other hand, the only patient who has shown a lasting remission, for which prolonged steroid therapy

might be held responsible, had reversible urinary changes, and renal function was normal throughout.

It is a pleasure to acknowledge our debt to Professor Dorothy Russell and Dr. P. G. I. Stovin for their help with the pathological details; to Professor C. V. Harrison for kindly furnishing us with necropsy findings in Case 1, and for the sections; and to Dr. J. H. Ross for performing the renal biopsies in Case 2. Finally, we are grateful for help received from several Medical Officers of the Royal Navy, and to the Medical Director-General of the Navy, Sir Cyril May, for his interest in the subject.

Summary

A description is given, with five illustrative examples, of a disease in which haemoptysis is the presenting symptom, with progressive glomerulonephritis as a later development. Four out of the five patients died. They were all male and between the ages of 17 and 22.

Serial renal biopsies in one case revealed an initial focal nephritis followed by a severe diffuse glomerulonephritis.

The close resemblance in the early stages between this syndrome and idiopathic pulmonary haemosiderosis is emphasized and discussed.

Reasons are given for believing that the condition is analogous to the Schönlein–Henoch syndrome.

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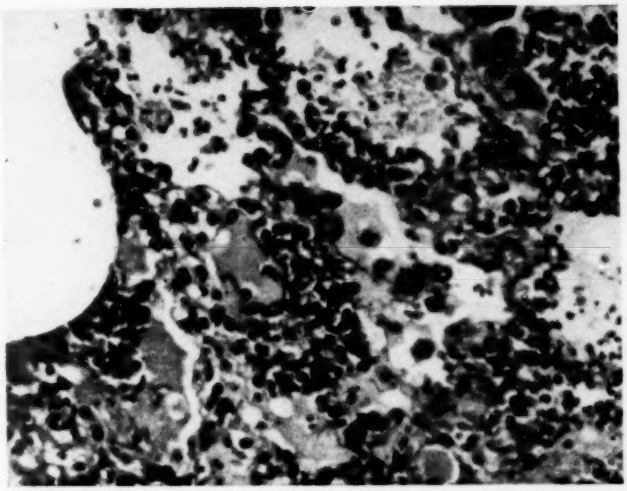

FIG. 1. Case 1, P. H. The section shows abundant red corpuscles with iron-laden macrophages in the alveoli. A little thin serous exudate is also present. The alveolar walls are intact
(Haematoxylin and eosin, ×264)

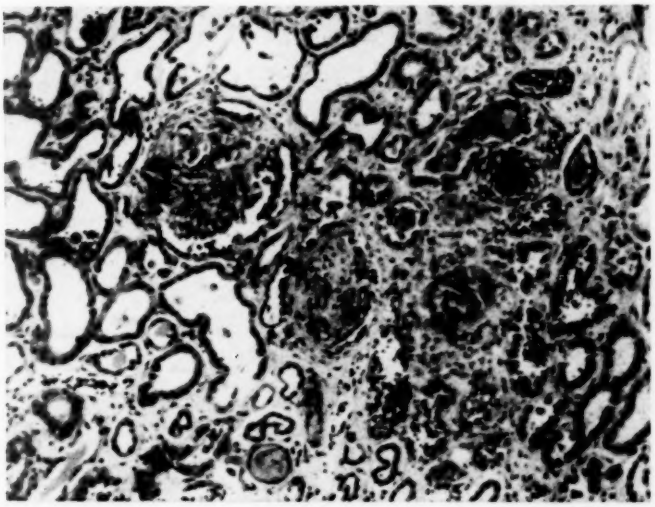

FIG. 2. Case 1, P. H. Section of the kidney showing hyaline necrosis of tufts, capsular adhesions, epithelial crescent formation, and tubules containing blood
(Haematoxylin and eosin, ×110)

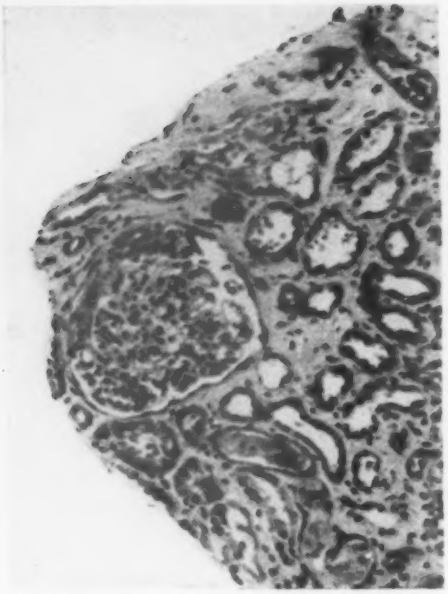

FIG. 3. Case 2, T. B. First renal biopsy (4.3.58). Glomerulus showing organized focal necrosis, with capsular adhesion and partial epithelial crescent
(Haematoxylin and eosin, ×145)

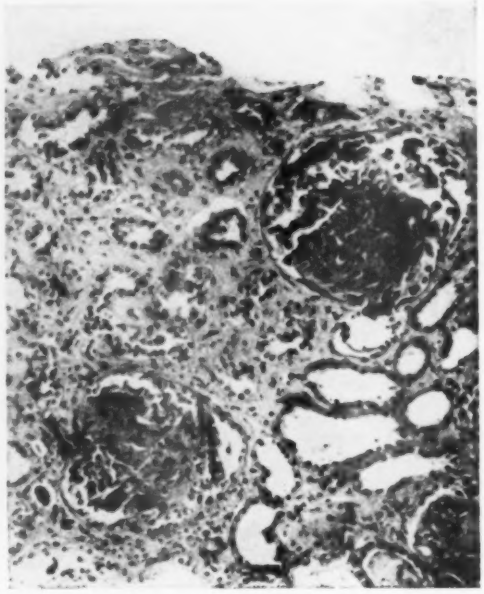

FIG. 4. Case 2, T. B. Second renal biopsy (15.4.58). Hyaline necrosis of glomerular tufts, capsular adhesions, and epithelial proliferation
(Contrast with fig. 3)

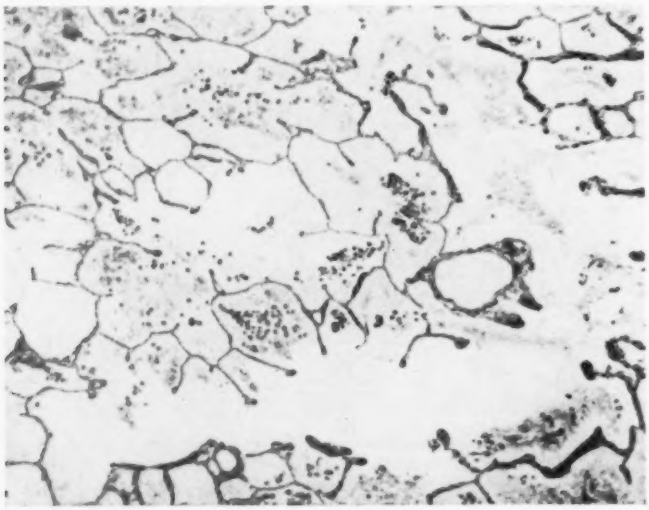

FIG. 5. Case 2, T. B. A respiratory bronchiole dividing into two branches. The reticulin pattern of these bronchioles and the adjacent alveoli is intact
(Gomori method, ×62)

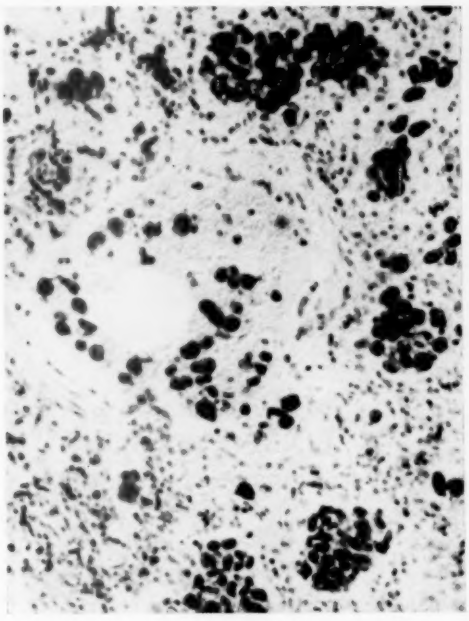

FIG. 6. Case 3, P. B. Section of lung stained to show free iron. Iron-laden macrophages in clumps in the alveoli and small bronchus (Perls' iron stain, × 164)

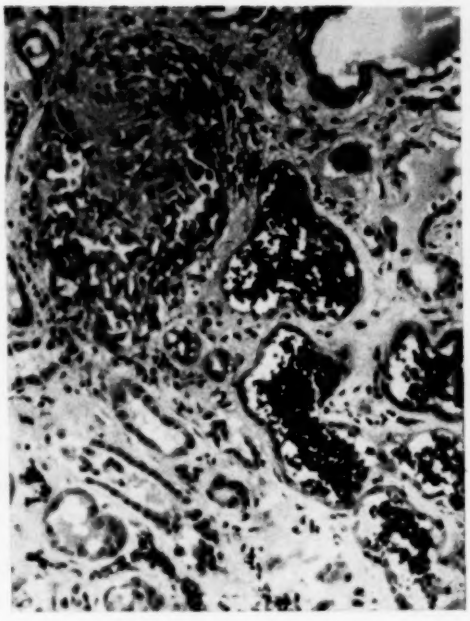

FIG. 7. Case 3, P. B. Section of kidney showing hyaline glomerular necrosis with epithelial crescent formation. Blood in tubular lumen (Haematoxylin and eosin, × 120)

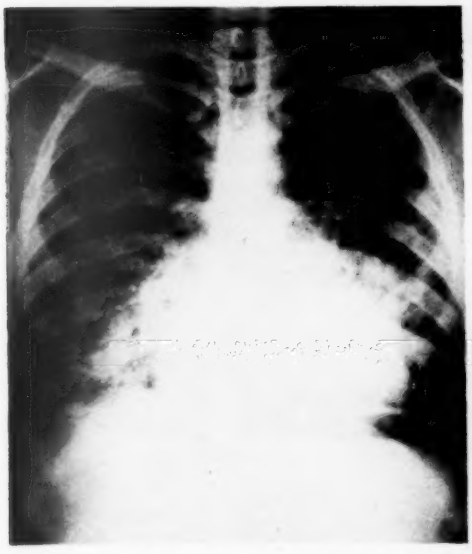

FIG. 8. Case 3, P. B. Lung changes at the height of haemoptysis (10.7.58)

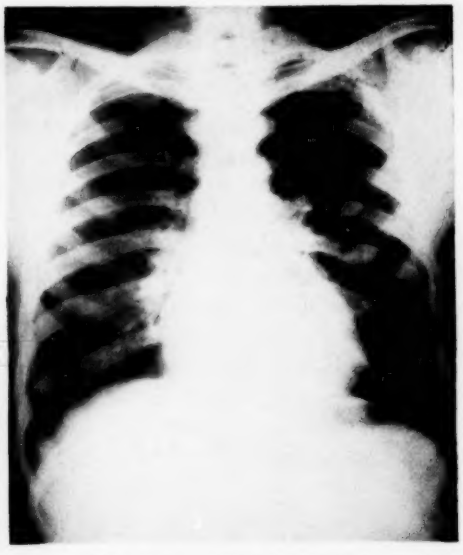

FIG. 9. The same patient 18 days later, when bleeding had stopped and clearing had taken place (28.7.58)

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ANAEMIA IN HYPOTHYROIDISM[1]

Incidence, Pathogenesis, and Response to Treatment

By G. R. TUDHOPE and G. M. WILSON

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With Plate 42

The association of anaemia with hypothyroidism has been repeatedly described since the end of the last century (Charcot, 1881; Bramwell, 1893; Emery, 1923; Holbøll, 1936). The nature of this anaemia was studied by Bomford (1938), who described three types: simple hyperchromic, hypochromic, and Addisonian hyperchromic anaemia. The latter two types he regarded as iron-deficiency and true pernicious anaemia occurring in association with myxoedema, without necessarily being causally related. He considered that the simple hyperchromic anaemia occurred in uncomplicated hypothyroidism, and suggested that it represented a decrease in the total mass of red cells, as a physiological compensation for the reduced rate of consumption of oxygen by the tissues. Anaemia was reported by Horsley in 1885 to follow removal of the thyroid in monkeys, and since then numerous studies have confirmed the fact that some relationship exists between experimental hypothyroidism and anaemia in animals (Kunde, 1926; Kunde, Green, and Burns, 1932; Sharpe and Bisgard, 1936; Gordon, Kadow, Finkelstein, and Charipper, 1946; Adam and Doljanski, 1958). In man a macrocytic hyperchromic anaemia was described after total thyroidectomy for congestive cardiac failure (Stern and Altschule, 1936). The association of true pernicious anaemia and hypothyroidism has been considered rare (Daughaday, Williams, and Daland, 1948). Wintrobe (1956) suggested that vitamin-B_{12} deficiency might result from impaired gastric secretion and loss of appetite, which commonly occur in hypothyroidism. Recently Leithold, David, and Best (1958) reported impairment of vitamin-B_{12} absorption, as measured by the urinary excretion test, in three out of seven patients with hypothyroidism. This defect in absorption was not corrected when intrinsic factor was given along with a test dose of labelled vitamin B_{12}. The gastric juice of two of these patients, tested in patients with pernicious anaemia, appeared to be deficient in intrinsic-factor activity. Leithold and his colleagues inferred that defective intestinal absorption of vitamin B_{12} sometimes occurs in hypothyroidism, because of a local block in intestinal absorption, or depressed secretion of intrinsic factor, or both. In rats the absorption of labelled vitamin B_{12} has been

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found to be significantly decreased after thyroidectomy; and in normal rats given desiccated thyroid orally for five weeks the absorption was greater than in control animals (Okuda, Steelman, and Chow, 1956).

Because of the descriptions of macrocytic anaemia in hypothyroidism, and the recent reports of impaired absorption of vitamin B_{12}, it was decided to investigate further the relationship between the absorption of vitamin B_{12} and the occurrence of anaemia in patients with hypothyroidism. In the course of this study it became evident that a surprisingly large number of these patients had true Addisonian pernicious anaemia. The effect of hypothyroidism on blood formation and the incidence of different types of anaemia were accordingly determined, and the haematological response to treatment with thyroxine or with haematinic agents has been investigated.

Patients Studied and Methods of Investigation

It was intended to include all patients sent to the Royal Infirmary, Sheffield, and referred to this department for radio-iodine tracer tests between January 1950 and April 1959, in whom the diagnosis of hypothyroidism was firmly established. In addition to the tracer test, the diagnosis was based on the clinical features, the level of serum cholesterol, and the basal metabolic rate; in most cases coming under observation since January 1958 the serum level of protein-bound iodine has also been determined (Acland, 1957, 1958). There were 166 patients with primary hypothyroidism, and an adequate examination of

TABLE I

The Cause of Hypothyroidism in 166 Cases, showing the Number of Cases in which Records were Available of Examination of the Blood

Cause of hypothyroidism	*Blood examined before starting treatment*	*Blood examined only after treatment*	*No blood findings available*	*Total number of cases*
Spontaneous primary hypothyroidism	79	15	3	97
Previous treatment for thyrotoxicosis with radio-iodine or X-radiation	32	18	14	64
Previous thyroidectomy	5	0	0	5
Total	116	33	17	166

the blood had been carried out before starting treatment in 116 of these cases; in 33 cases the blood was not examined until after treatment with thyroid or thyroxine had been started, and in 17 there was no record of blood examination. The aetiology of the hypothyroidism is shown in Table I. Patients with hypothyroidism following ^{131}I therapy of thyrotoxicosis were included only if continued observations had confirmed the permanent nature of the condition, as in some it may be only a temporary feature (Blomfield, Eckert, Fisher, Miller, Munro, and Wilson, 1959). The haematological studies were not carried out until its permanent nature was fully established. Patients with hypothyroidism secondary to hypopituitarism were not included in the study. More detailed

TABLE II

The Condition of the Blood and the Evidence of Hypothyroidism in 30 patients in whom Studies of Vitamin-B_{12} Absorption, Red-cell Survival, or Blood Volume were made

Case number	*Age (years)*	*Sex*	*Condition of blood*	*Type of hypothyroidism*	*Serum protein-bound iodine (μg./100 ml.)*	*Thyroid uptake of ^{131}I (%)*		*'T' index†*	*Basal metabolic rate (%)*	*Serum cholesterol (mg./100 ml.)*
						4-hr.	*24-hr.*			
1	46	F	Normal	Idiopathic	1·40	16·0	19·9	3·8	−20	565
2	46	F	,,	,,	0·95	4·0	8·6	..	−30	590
3	47	F	,,	,,	0·60	0·6	1·1	..	−18	270
4	65	F	,,	,,	1·20	4·8	7·0	..	..	400
5	43	F	,,	Post-^{131}I	0·95	6·3	11·1	..	..	490
6	54	F	,,	,,	1·30	5·0	5·8	..	−30	320
7	33	F	,,	,,	1·10	4·0	6·2	3·6	−20	395
8	45	M	,,	,,	..	2·1	3·3	1·2	−31	370
9	50	F	,,	,,	..	11·7	16·4	..	..	455
10	63	F	,,	,,	..	9·6	11·2	..	..	465
11	66	M	,,	,,	1·80	5·2	1·7	..	−22	535
12	68	F	,,	,,	..	5·5	9·7	..	..	250
13	60	F	,,	,,	..	0·0	0·0	1·1	−18	480
14	55	F	,,	,,	..	7·5	6·4	..	..	573
15	65	M	,,	,,	..	11·7	27·1	..	..	520
16	68	F	Normocytic anaemia	Idiopathic	..	8·6	12·2	1·3	−28	375
17	48	M	,,	,,	..	7·3	12·7	..	..	349
18	38	F	Iron deficiency	,,	..	3·8	7·0	..	..	352
19	52	F	,,	,,	1·35	4·4	10·7	..	−10	310
20	32	F	,,	,,	1·15	10·1	26·2	0·4	−27	390
21	38	F	,,	,,	0·70	4·2	1·7	2·4	−33	355
22	56	F	,,	Post-^{131}I	..	7·9	11·4	1·4	−14	340
23	43	M	Vitamin-B_{12} deficiency	Idiopathic	2·05	6·3	4·6	..	−16	410
24	72	F	,,	,,	1·15	6·2	4·5	..	−39	250
25	54	M	,,	,,	1·80	0·3	0·0	3·3	..	335
26	67	F	,,	,,	..	..	..	..	−14	450
27	58	F	,,	,,	..	5·8	0·0	1·8	..	485
28	62	M	,,	,,	..	5·2	0·0	..	−21	400
29	46	F	* ,,	,,	1·05	21·1	27·5	3·5	−19	315
30	30	F	,,	Post-thyroidectomy	..	0·0	0·0	1·1	−22	310

* Case 29. Vitamin-B_{12} deficiency without anaemia (see text).
† *T* index calculated as described by Fraser (1956). The normal range is 2·8 to 13.

investigations were carried out in 30 of these cases, in which the evidence supporting the diagnosis of hypothyroidism is shown in Table II.

The absorption of an oral dose of labelled vitamin B_{12}, with and without added intrinsic factor, was studied by the urinary excretion test (Schilling, 1953; Schilling, Clatanoff, and Korst, 1955; Callender and Evans, 1955*a*; Best, White, Robbins, Landmann, and Steelman, 1956). Vitamin B_{12} labelled with ^{56}Co (original specific activity 2·75 μc. per μg.) was used in investigating five cases; in the other cases the isotope used was ^{58}Co (original specific activity 3·37 μc. per μg.). The labelled vitamin B_{12} was given in the morning, the patient having fasted for at least 12 hours, and no food or drink was allowed for a further two hours. The dose given in each test was 0·5 μg.; this was diluted in 100 ml. of water, and given as a drink. The drinking-glass was washed out twice with water, and the washings were also drunk. Simultaneously with the oral dose of labelled vitamin B_{12}, an intramuscular injection of 1 mg. of unlabelled vitamin B_{12} was given. All urine was collected for 24 hours, the volume was measured, and duplicate samples were taken for the measurement of radioactivity. In each test duplicate standard dilutions were prepared with distilled water, from the residue of the solution of labelled vitamin B_{12}, after the oral dose had been given. The radioactivity of all samples and standard dilutions was measured with a scintillation counter. The total activity excreted in the urine in 24 hours was expressed as a percentage of the administered activity. The intrinsic factor used was a powdered preparation from hog's duodenum, supplied by Armour Laboratories Ltd. A suspension was made of 100 mg. of the powder in 50 ml. of water, half of this being drunk just before the oral dose of labelled B_{12} and the remainder immediately afterwards.

Total red-cell volume was measured by the injection of the patient's red cells, labelled with ^{51}Cr (Mollison and Veall, 1955). The survival of red cells was studied from observations of the ^{51}Cr activity in the circulating blood during a period of nine to 15 days after the injection of labelled cells, blood samples being taken at intervals of two to five days (Read, Wilson, and Gardner, 1954). Observations of ^{51}Cr survival were compared with the findings previously obtained in 10 normal subjects (Tudhope, 1958).

Plasma volume was measured by the dye-dilution technique, using Evans blue (Reeve, 1948; Barnes, Loutit, and Reeve, 1949), with extraction of the dye on a cellulose column, by the method of Bedwell, Patterson, and Swale (1955) as modified by Verel (1957).

Utilization of radio-iron (Finch, Gibson, Peacock, and Fluharty, 1949; Bothwell, Callender, Mallett, and Witts, 1956). To about 10 ml. plasma were added 5 to 10 μc. ^{59}Fe (0·1 to 0·2 ml. $^{59}FeCl_3$ solution), and the mixture was allowed to stand for 20 minutes at room temperature. Five ml. of the labelled plasma were then injected intravenously. Blood samples were taken at intervals of two to four days for 13 to 17 days. From the radioactivity of each blood sample, the red-cell utilization was expressed as a percentage of the administered amount of ^{59}Fe, the total red-cell volume having been previously determined with ^{51}Cr.

Biopsy of gastric mucosa was carried out in seven patients, using Wood's flexible gastric biopsy tube (Wood, Doig, Motteram, and Hughes, 1949; Joske, Finckh, and Wood, 1955), and following the technique of these workers. Two fragments of gastric mucosa were obtained in most cases; the disks of mucosa, of about 2 mm. diameter, were fixed in 10 per cent. formol saline and embedded in paraffin. No haemorrhage or other untoward effect occurred.

The concentration of serum iron was measured by the method of Ramsay (1953), as modified by the same author in 1954. The normal range of serum iron concentration was found by Ramsay (1953) to be 112 to 255 μg. per 100 ml. for male and 78 to 170 μg. per 100 ml. for female subjects.

Serum vitamin B_{12}. The estimations of vitamin B_{12} in serum were performed by Dr. G. H. Spray in Oxford. Blood was withdrawn in all-glass syringes and transferred to specially prepared acid-cleaned bottles. After clotting was complete the bottles were centrifuged, and the serum was removed and stored in a deep-freeze. Assay of vitamin B_{12} was by a microbiological method, using *Lactobacillus leichmannii* (Spray, 1955). The results are expressed as $\mu\mu$g. of vitamin-B_{12} activity per ml. of serum. Using this method, Spray and Witts (1958) reported that the values in 123 normal subjects ranged from 150 to 1,000 $\mu\mu$g. per ml., with a mean of 450 $\mu\mu$g. per ml. They found values of 100 $\mu\mu$g. per ml. or less in 85 out of 94 patients with pernicious anaemia in relapse; in seven patients the values were between 100 and 170 $\mu\mu$g. per ml.

Serum protein-bound iodine was estimated by Dr. R. Kilpatrick in the Department of Pharmacology, University of Sheffield, using the method of Acland (1957, 1958). The normal range by this technique has been found to be 3·5 to 8·0 μg. per 100 ml. (Kilpatrick, 1959); this is similar to the results obtained by other workers (Starr, Petit, Chaney, Rollman, Aiken, Jamieson, and Kling, 1950; Fraser, 1956). All results quoted are the mean of two estimations.

Radio-iodine studies of thyroid function were performed by the method described by Goodwin, Macgregor, Miller, and Wayne (1951). In this department the mean four-hour thyroid uptake of ^{131}I in 125 normal subjects was 24·3 per cent. of the dose (S.D. $\pm$ 7·2 per cent.). The normal range for the 24-hour uptake is reported as 10–40 per cent. of the dose, but there is an overlap between values obtained in normal subjects and those found in persons with mild hypothyroidism (Werner, Hamilton, Leifer, and Goodwin, 1950; McConahey, Owen, and Keating, 1956).

Basal metabolic rate was estimated with the standard Benedict–Roth apparatus; the figures quoted are the mean of four results. Estimations were carried out only with in-patients, who had been resting in bed and fasting for 12 hours before the test. Surface area was calculated from the patient's weight and height (Du Bois and Du Bois, 1916). Basal metabolism, as measured by oxygen consumption, was expressed as a percentage deviation from the normal mean, using the standards of Boothby, Berkson, and Dunn (1936).

Blood films were examined by one of two haematologists, who knew that the blood samples came from patients with hypothyroidism, but were not aware of the other laboratory findings. The red cells were described as

normocytic, macrocytic, or microcytic on the basis of their appearance alone. No direct measurements of red-cell size were carried out. An anaemia was thus classified as macrocytic only if this was apparent from the blood film.

Results

The haematological diagnoses in 116 cases of untreated hypothyroidism are shown in Table III. For the purpose of this classification patients were regarded as anaemic when the level of haemoglobin was less than 12·0 g. per 100 ml. in women, and less than 13·9 g. per 100 ml. in men. These values are based on the range of haemoglobin levels observed in normal subjects by Wintrobe (1933). Similar results for the range of haemoglobin values in normal adults have more recently been found in the United States (Morris, Loy, Strutz, Schloesser, and Schilling, 1956) and in Great Britain (Berry, Cowin, and Magee, 1952).

TABLE III

Haematological Diagnoses in 116 Patients with Untreated Hypothyroidism

Haematological diagnosis	*Number of cases*
Normal	79
Normocytic anaemia	5
Microcytic anaemia	17
Pernicious anaemia	13
Other macrocytic anaemia	2
Total	116

Non-anaemic patients and normocytic anaemia

In 84 cases the blood film showed normocytic red cells. The levels of haemoglobin in these cases are shown in Fig. 1. In this group only five patients (four

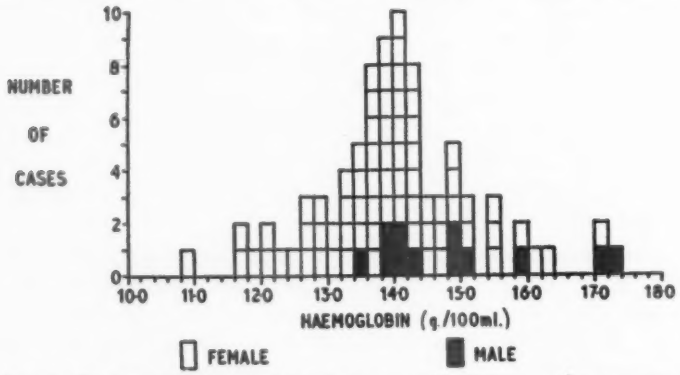

FIG. 1. The levels of haemoglobin in 84 patients who were suffering from untreated hypothyroidism and whose red cells appeared normocytic.

female, one male) were anaemic by the criteria stated, and the anaemia was mild in degree. No cause of anaemia other than hypothyroidism was detected, and the serum levels of iron and vitamin B_{12} were within the normal ranges.

In two of these patients the marrow was examined, and in both it appeared hypocellular but otherwise normal. When treatment was given with thyroxine alone, the level of haemoglobin increased to normal in one to four months (Fig. 2). Although in each case the film of the peripheral blood appeared normal, and no macrocytosis was observed, in one of these patients with mild

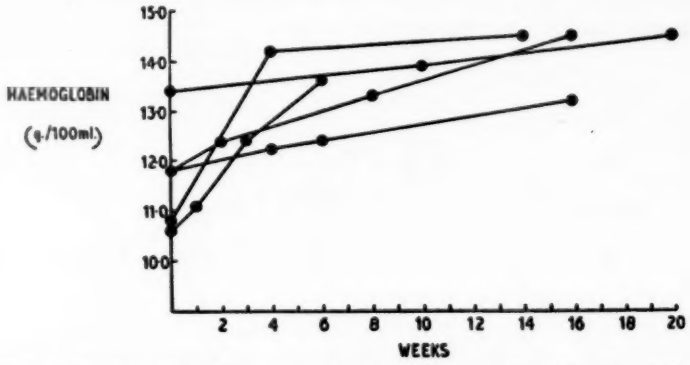

FIG. 2. Five cases of mild normocytic anaemia in hypothyroidism, in which there was no evidence of deficiency of iron or of vitamin B_{12}. The haemoglobin increased to normal during treatment with thyroxine alone.

anaemia the mean corpuscular volume was abnormally great, being 100 cu. μ initially and decreasing to 92 cu. μ after treatment. In two other patients with mild anaemia the mean corpuscular volume decreased after treatment, but the values before treatment were not outside the normal range. These observations are consistent with the findings of Bomford (1938). The patients showing the lower haemoglobin values in Fig. 1 have been compared with the others higher on the scale, but there was no evidence that the development of the anaemia was related to the severity, duration, or aetiology of the hypothyroidism.

TABLE IV

Total Red-cell and Plasma Volumes Before and After Treatment with Thyroxine in Six Patients with Hypothyroidism

Case number	*Age (years)*	*Sex*	*Haemoglobin (g./100 ml.)*		*Total red-cell volume (litres)*		*Plasma volume (litres)*	
			Before	*After*	*Before*	*After*	*Before*	*After*
12	68	F	13·6	13·8	1·47	1·68	2·31	2·59
13	60	F	15·4	14·8	1·71	1·86	3·01	3·19
14	55	F	13·0	15·1	1·36	1·45	2·38	2·29
15	65	M	14·5	14·1	1·84	1·83	3·32	3·32
16	68	F	11·8	13·2	1·19	1·42	2·40	2·33
17	48	M	13·4	14·5	1·74	2·05	3·35	3·39

The total red-cell and plasma volumes were measured in six patients with normocytic red cells (Cases 12 to 17, Tables II and IV). The total red-cell volume increased after treatment of the hypothyroidism in five patients. In two (Cases 12 and 13) the plasma volume also increased; these two patients

were not anaemic when hypothyroid, and the haemoglobin showed no significant change after treatment. In the other three patients in whom the red-cell volume increased, the plasma volume was not significantly altered after treatment, and in these cases the haemoglobin increased after correction of the hypothyroid state. One patient (Case 15) who was not anaemic, and who had only a mild degree of hypothyroidism, showed no change in total red-cell volume or in plasma volume after treatment.

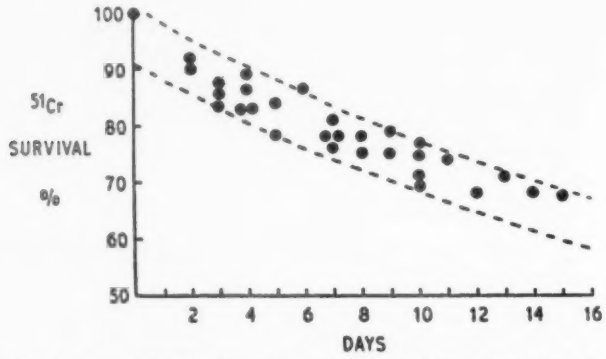

FIG. 3. Survival of red cells by the ^{51}Cr-labelling technique in eight patients with hypothyroidism. Six were not anaemic, one had normocytic anaemia, and one microcytic anaemia. The broken lines indicate the range of values observed in 10 normal subjects.

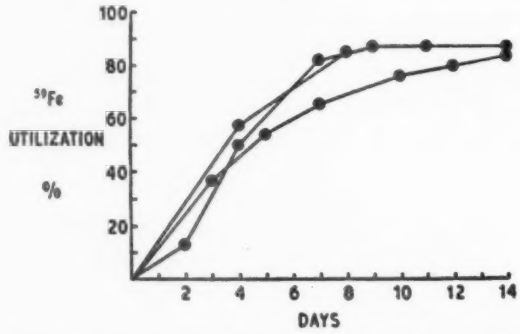

FIG. 4. Normal utilization of a tracer dose of radio-iron in three patients with hypothyroidism. In normal subjects the utilization is 75 to 90 per cent. at seven to 12 days after injection.

The survival of red cells, studied by the ^{51}Cr technique (Fig. 3), was normal in six hypothyroid patients who were not anaemic (Cases 4 and 10 to 14) and in one who had mild normocytic anaemia (Case 16).

The utilization of radio-iron was measured in three patients (Fig. 4), of whom two were not anaemic (Cases 11 and 13) and one had normocytic anaemia (Case 16). In normal subjects the red-cell utilization of radio-iron is 75 to 90

per cent. at seven to 12 days after injection (Bush, Ashenbrucker, Cartwright, and Wintrobe, 1956; Weinstein and Beutler, 1955; Bothwell, Callender, Mallett, and Witts, 1956), and the results in the hypothyroid patients fell within this range.

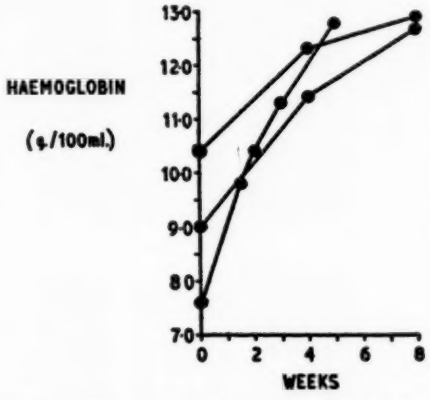

FIG. 5. Three cases of hypothyroidism with hypochromic microcytic anaemia. The level of haemoglobin increased rapidly during treatment with iron alone, while the patients remained hypothyroid.

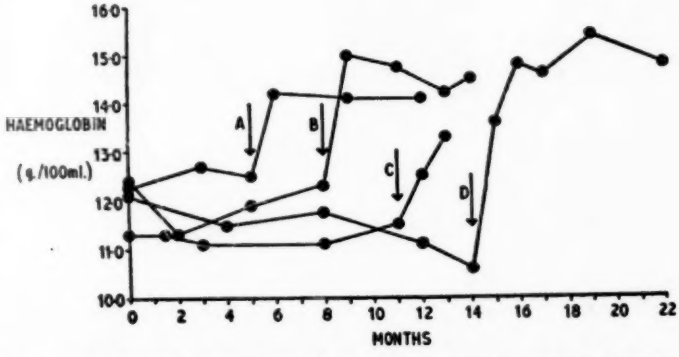

FIG. 6. Four cases of hypothyroidism with microcytic anaemia. During treatment with thyroxine there was no increase in haemoglobin, but the addition of oral iron therapy (indicated by the arrows) resulted in a rapid haematological response.

Microcytic anaemia

The red cells in the peripheral blood film were microcytic in 17 cases. In six patients severe menorrhagia, chronic sepsis, or rheumatoid arthritis were present, and the anaemia responded only slowly and inadequately during treatment with thyroxine and oral iron. There were no complicating features in 11 patients, in whom the levels of haemoglobin were in the range 7·4 g. to 12·4 g.

TABLE V

Details of 13 Patients with Coexisting Hypothyroidism and Pernicious Anaemia

Case number	*Sex*	*Age at diagnosis of pernicious anaemia (years)*	*Time relationship*	*Type of hypothyroidism*	*Evidence of hypothyroidism*	*Evidence of pernicious anaemia*
23	M	43	Diagnosed together	Idiopathic	See case report and Table II	See Table VIII
24	F	72	,,	,,	,, ,, ,,	,, ,,
25	M	54	Hypothyroidism first by 6 yrs.	,,	,, ,, ,,	,, ,,
26	F	67	Hypothyroidism first by 1 yr.	,,	Typical clinical features of myxoedema confirmed by investigations (Table II). Macrocytes in blood film. Only partial response to thyroxine: disappearance of cutaneous features and loss of weight. Angina pectoris and congestive failure developed	9 months after beginning thyroxine pallor and limb paraesthesiae developed. Laboratory findings (Table VIII). Reticulocytosis (15%) followed vitamin B_{12}. All symptoms relieved by combined therapy. Haemoglobin increased to 13·8 g./100 ml.
27	F	58	Pernicious anaemia first by 7 yrs.	,,	See case report and Table II	See Table VIII
28	M	62	Pernicious anaemia first by 12 yrs.	,,	,, ,, ,,	,, ,,
30	F	30	Hypothyroidism first by 3 yrs.	Post-thyroidectomy	Typical clinical features developed 3 yrs. after removal of thyroid swelling: histology of thyroid not available. Laboratory investigation (Table II). Some response to thyroid medication, but lassitude persisted. Relapse on stopping thyroid	Pallor, paraesthesiae in limbs, smooth sore tongue. Laboratory investigations (Table VIII). Good response to vitamin B_{12} alone, haemoglobin rising to 13·7 g./100 ml. Thyroid therapy then restarted
31	M	46	Hypothyroidism first by 1 yr.	Idiopathic	Typical clinical features. Low-voltage electrocardiogram. Serum cholesterol 268 mg./100 ml. Good response to thyroid	Pallor, icterus, paraesthesiae, splenomegaly. Haemoglobin 5·6 g./100 ml. Red cells 1·2 mill./cu. mm. Megaloblastic marrow. Achlorhydria. Reticulosis (10%) and haemoglobin rising to 15·4 g./100 ml. following vitamin B_{12}
32	F	50	Pernicious anaemia first by 3 yrs.	,,	Definite clinical features. Serum cholesterol 520 mg./100 ml. Good response to thyroxine, and recurrence on stopping	Pallor, icterus, paraesthesiae in hands and feet. Haemoglobin 7·3 g./100 ml. Red cells 1·75 mill./cu. mm. Macrocytosis. Good response to liver extract, haemoglobin rising to 14·1 g./100 ml.

33	F	56	Hypothyroidism first by 30 yrs.	„	Myxoedema diagnosed on clinical features in 1926; ever since treated with thyroid with relief of symptoms. On stopping thyroid for 4 weeks in 1956 features of myxoedema appeared: ^{131}I uptake negligible and no response to thyroid-stimulating hormone. Basal metabolic rate −13%	Pallor, splenomegaly. Haemoglobin 7·7 g. per 100 ml. Red cells 2·3 mill./cu. mm. Megaloblastic marrow. Achlorhydria. Good response to vitamin B_{12}, haemoglobin rising to 13·1 g./100 ml.
34	F	54	Pernicious anaemia first by 10 yrs.	„	Intolerant of cold; hoarse voice, lassitude, but no definite skin changes. Serum cholesterol 412 mg./100 ml. ^{131}I uptake $< 5\%$. *T* index 2·2. Good response to thyroxine	Sore tongue, slight icterus. Haemoglobin 10·0 g./100 ml. Megaloblastic marrow. Achlorhydria. Haemoglobin rose to 14·0 g./100 ml. after liver-extract therapy
35	F	38	Pernicious anaemia first by 7 yrs.	Post-radiotherapy	Deep X-ray therapy for goitre when aged 30 yrs.; became hypothyroid at 45 yrs. ^{131}I uptake 4%. Serum cholesterol 370 mg./100 ml. Thyroid tissue completely fibrotic at autopsy	Pallor, slight icterus, smooth tongue. Haemoglobin 8 g./100 ml. Red cells 2·15 mill./cu. mm. Response to liver extract and later vitamin B_{12}. Histamine-fast achlorhydria
36	F	54	Pernicious anaemia first by 3 yrs.	Post-^{131}I therapy	Partial thyroidectomy for thyrotoxicosis when aged 47 yrs. Recurrence 6 mths. after operation, treated with methyl thiouracil for 3 years. Further recurrence at 57 yrs. treated with ^{131}I; became hypothyroid 2 mths. later, showing definite features of myxoedema	Pallor; haemoglobin 11·3 g./100 ml.; red cells 3·62 mill./cu. mm.; macrocytosis. Megaloblastic marrow. Achlorhydria. Good response to vitamin B_{12}, haemoglobin rising to 14·8 g./100 ml.

per 100 ml. In three of these 11 cases, in which the red cells showed conspicuous hypochromia and microcytosis and the haemoglobin level was from 7·8 g. to 10·4 g. per 100 ml., treatment with iron alone was given for five to eight weeks before starting treatment with thyroxine. In each case there was a prompt haematological response while the patient was still hypothyroid (Fig. 5).

Four patients of this group, who had a moderate degree of microcytic anaemia (haemoglobin 11·3 g. to 12·4 g. per 100 ml.), and in whom the level of serum iron was only moderately reduced (44 μg. to 65 μg. per 100 ml.), were treated for five to 14 months with thyroxine alone; there was no increase in haemoglobin, and in one patient the serum iron decreased to 20 μg. per 100 ml. Oral iron therapy was then started, and the haemoglobin level rapidly increased (Fig. 6). The red-cell survival was measured in one of these cases of microcytic anaemia (Case 21), and was normal (Fig. 3).

Pernicious anaemia

Classical pernicious anaemia was present in 13 cases. The evidence for both diagnoses is summarized in Table V. Spontaneous hypothyroidism was present in 10 of these patients. In one patient (Case 30) hypothyroidism followed operation for removal of a thyroid swelling, but unfortunately it has not been possible to trace any histological examination of the excised tissue, or to determine the nature of the abnormality in the gland. In Case 35 the radiotherapy was probably given for thyrotoxicosis, as the patient stated that she had a goitre associated with protruding eyes, but it has not been possible to trace any record. The presence of thyrotoxicosis was firmly established in Case 36 before the ^{131}I therapy was given. In two patients the diagnosis of both conditions was made together (Cases 23 and 24). In Case 26 the symptoms were not fully relieved by thyroxine, and the macrocytosis, initially regarded as due to the hypothyroidism, persisted until vitamin B_{12} was given. Probably both conditions were present at the same time, though the pernicious anaemia was not recognized until a year later. In Case 30 the pernicious anaemia was not diagnosed until three years after the hypothyroidism, but in this patient also the response to treatment with thyroid was not wholly satisfactory until vitamin B_{12} was given. In the other cases the presentation of the two conditions was more clearly separated. The initial response to treatment of pernicious anaemia with vitamin B_{12} in the presence of established hypothyroidism was observed in four patients (Cases 23, 24, 25, and 30). Treatment with vitamin B_{12} alone was given for three to four weeks before thyroxine was administered. During that time the blood became completely normal in three patients, and in the fourth (Case 24, detailed below) there was a rapid haematological response, but thyroxine was given before the blood had fully returned to normal.

The following case histories illustrate different types of clinical presentation when pernicious anaemia and hypothyroidism occur together. The first case to be described is of interest because of the initial difficulty in diagnosis.

Case 23. A riveter, aged 43 years, had complained of tiredness, lack of energy and interest, slowness of speech, numbness of the feet, occasional diplopia, and constipation, for about five years. He was at first admitted to a neurosurgical ward, as the possibility of cerebral tumour had been considered. There was general pigmentation of the skin, and one patch of pigmentation on the buccal mucosa. The skin was scaly and thick, and the hair was coarse. His appearance was suggestive of hypothyroidism, and convincing evidence for this diagnosis was obtained (Table II). Examination of the blood showed a normal level of haemoglobin (14·3 g. per 100 ml.), but the red-cell count was 3·1 millions per cu. mm., and macrocytosis was evident. Megaloblastic erythropoiesis was found in the marrow, the level of vitamin B_{12} in the serum was very low, and the gastric mucosa was atrophic (Plate 42, Fig. 7). There was failure of absorption of labelled vitamin B_{12}, corrected by intrinsic factor (Table VIII). He was treated initially with vitamin B_{12}, and there was a small reticulocytosis (5 per cent.) and a decrease in serum iron from 130 μg. to 40 μg. per 100 ml., four days after the first injection of vitamin B_{12}. Treatment with vitamin B_{12}, without thyroxine, was continued for one month, at the end of which the marrow had become normal, and the peripheral blood was also normal (haemoglobin 16·6 g. per 100 ml., red cells 4·7 millions per cu. mm.). Thyroxine therapy was then started, and his symptoms gradually disappeared. Vitamin-B_{12} absorption, when studied again five months later, was still depressed.

In the following case the diagnosis was much less difficult, as the typical clinical features of both conditions were present.

Case 24. A housewife, aged 72 years, was admitted to hospital with a history of tiredness, hypersensitivity to cold, sore tongue, and frequent 'blackouts', for one year. She had noticed dryness of the skin and loss of hair for a few years. Her appearance suggested hypothyroidism, and this diagnosis was confirmed (Table II). The changes typical of pernicious anaemia were also found (Table VIII). She was treated initially with vitamin B_{12}, and in 22 days haemoglobin had risen from 10·6 g. to 12·4 g. per 100 ml., and red cells from 2·45 to 4·0 millions per cu. mm. Treatment with thyroxine was then started, and the signs and symptoms of hypothyroidism gradually disappeared. Five months later, when she was euthyroid, the absorption of vitamin B_{12} was still low, in the range found in pernicious anaemia. In this case treatment with vitamin B_{12} resulted in a prompt and rapid haematological response, but thyroxine was given before the blood had returned to normal, because of the severity of the myxoedema.

The association of hypothyroidism with angina due to coronary artery disease is frequently a difficult therapeutic problem. In the following case, however, the angina resulted from concomitant pernicious anaemia, and with correction of the anaemia adequate thyroxine could be given without causing angina.

Case 25. A colliery manager had myxoedema in 1951, and was subsequently free from symptoms for five years while taking thyroid tablets. In June 1957, when aged 54 years, he complained of increasing tiredness and retrosternal pain on exertion. Thyroid medication had been stopped one month previously because of the anginal pain. The changes typical of pernicious anaemia were found (Table VIII), except that the gastric mucosa did not show the gross atrophy usually found in that condition, and a few oxyntic cells were present

(Plate 42, Fig. 8). Treatment with vitamin B_{12}, without further thyroid administration, resulted in the peripheral blood returning to normal in six weeks, haemoglobin increasing from 9·3 g. to 14·6 g. per 100 ml. and red cells from 2·9 to 4·3 millions per cu. mm. By this time, however, his appearance suggested hypothyroidism, and this diagnosis was confirmed (Table II). He was then treated with thyroxine, with great clinical improvement and without return of angina.

Two patients developed hypothyroidism while under treatment for pernicious anaemia. In one (Case 27) there was no change in the level of haemoglobin or the red-cell count, but in the other (Case 28), the haematological response to treatment with vitamin B_{12} was impaired while the patient showed evidence of hypothyroidism.

Case 27. A housewife, aged 58 years, was found to have pernicious anaemia in 1949. The diagnosis was based on macrocytic anaemia, megaloblastic erythropoiesis, histamine-fast achlorhydria, and an adequate haematological response to liver therapy. She remained reasonably well until 1955, when she began to have attacks of biliary colic, and cholecystectomy was performed in February 1956. After the operation she complained of increasing tiredness, and weakness; but the peripheral blood remained normal, marrow biopsy showed normoblastic erythropoiesis, and treatment with vitamin B_{12} was continued. When seen in September 1956 she was myxoedematous in appearance, and the presence of hypothyroidism was confirmed (Table II). The haemoglobin level and red-cell count had shown no significant change. Vitamin-B_{12} absorption tests at that time showed the typical findings in pernicious anaemia (Table VIII). She was treated with thyroxine, with complete relief of symptoms.

Case 28. A labourer, aged 62 years, was found to have pernicious anaemia in 1945. The diagnosis was based on macrocytic anaemia (haemoglobin 5·0 g. per 100 ml., red cells 1·3 millions per cu. mm.), megaloblastic erythropoiesis, histamine-fast achlorhydria, and good haematological response to liver extract. The blood remained normal until 1955, when he was receiving vitamin B_{12}, 100 μg. fortnightly. From 1945 to 1955 the red-cell count had always been in the range 4·3 to 5·4 millions per cu. mm. During 1955 and 1956 the red-cell count fluctuated between 3·5 and 4·5 millions per cu. mm., and in 1957 it was persistently below 4·0 millions per cu. mm., in spite of regular injections of vitamin B_{12}. It then became apparent that the patient was suffering from hypothyroidism. His appearance, voice, and skin were compatible with that diagnosis. Radioiodine tests, basal metabolic rate, and serum cholesterol were all in the ranges associated with hypothyroidism (Table II). Treatment with thyroxine was started in December 1957. The peripheral blood remained unchanged until February 1958. The haemoglobin and red-cell count steadily increased during the next three months, and in May 1958 the blood was repeatedly shown to be normal (red cells 4·5 to 4·8 millions per cu. mm.).

In the present series of 166 cases of hypothyroidism there were 13 cases of pernicious anaemia. Pernicious anaemia was found more frequently in patients with spontaneous hypothyroidism (10·3 per cent.) than in those who developed hypothyroidism after partial thyroidectomy or radiation therapy (Table VI). For comparison, in a group of 760 patients with thyrotoxicosis who had received

radio-iodine treatment at the Royal Infirmary, Sheffield, the incidence of pernicious anaemia was 1·2 per cent. (Table VI). These patients were mostly aged over 45 years, and so were of a similar age group to the hypothyroid cases. As a further comparison, figures were obtained of the number of patients

TABLE VI

The Incidence of Pernicious Anaemia in Cases of Hypothyroidism, in Cases of Thyrotoxicosis, and in the General Population

	Total number of persons	*Cases of pernicious anaemia*	*Incidence of pernicious anaemia (%)*
Hypothyroidism:			
(*a*) all cases	166	13	7·8
(*b*) spontaneous hypothyroidism	97	10	10·3
(*c*) following partial thyroidectomy or radiation therapy	69	3	4·3
Thyrotoxicosis	760	9	1·2
General population (aged 45+ years)	12,639	44	0·35

TABLE VII

The Incidence of Pernicious Anaemia in Persons Aged 45+ Years in Eight Selected General Practices

Figures from the 1951 Census were used to calculate the number of persons aged 45 years and more from the total number in each practice

Practice	*Number of patients in practice*	*Number of patients aged 45+ years*	*Number of cases of pernicious anaemia*	*Incidence of pernicious anaemia in persons aged 45+ years (%)*
1	2,400	804	6	0·7
2	2,050	687	5	0·7
3	9,500	3,182	15	0·5
4	4,000	1,340	5	0·4
5	5,580	1,869	5	0·3
6	5,300	1,776	4	0·2
7	3,000	1,005	2	0·2
8	5,900	1,976	2	0·1
Total	37,730	12,639	44	0·35

receiving treatment for pernicious anaemia in eight selected general practices in the Sheffield region. There were 44 patients with pernicious anaemia, all of whom were aged 45 years or more. By applying the age-distribution figures of the 1951 Census to the total number of patients in these practices, the number aged 45 years and more was calculated; the mean incidence of pernicious anaemia in this age group was 0·35 per cent., and did not exceed 0·7 per cent. in any practice (Table VII).

Macrocytic anaemia other than pernicious anaemia

This form of anaemia was found in two patients at the time of diagnosis of hypothyroidism. One had cirrhosis of the liver with oesophageal varices, and

had suffered repeated haematemeses. The bone marrow showed macronormoblastic erythropoiesis, and the serum level of vitamin B_{12} was normal. The abnormalities of blood and marrow appeared to be adequately accounted for by the hepatic disease. The macrocytic anaemia was uninfluenced by thyroxine treatment. The second patient had gastric ulceration, and haemorrhage had recently occurred. Macrocytosis of the peripheral blood was found, and there were macronormoblasts in the marrow. The macrocytic anaemia was attributed to the gastric haemorrhage, and the blood returned to normal with cessation of the bleeding. Thyroxine therapy, however, had been started, so that the possible relationship of the macrocytosis and the hypothyroid state remained uncertain.

The Absorption of Vitamin B_{12}

Hypothyroidism without evidence of vitamin-B_{12} deficiency. In 12 patients (Cases 1 to 3, 5 to 9, 18 to 20, and 22), when the test of vitamin-B_{12} urinary excretion was performed, 10 per cent. or more of the oral dose of labelled vitamin B_{12} was detected in the urine in 24 hours (Table VIII). This is interpreted as indicating normal absorption of vitamin B_{12}; but in five of these patients the 24-hour urinary excretion was 10 to 15 per cent., which is at the lower limit of the normal range. The serum vitamin-B_{12} level was within the normal range in the eight cases in which it was estimated. Gastric biopsy, performed in three cases, showed no mucosal atrophy, but some degree of superficial gastritis was present in two. Gastric acidity was normal in six patients; in four there was histamine-fast achlorhydria. There was evidence of associated iron deficiency in four patients; in the remaining eight the peripheral blood was normal. The marrow was normoblastic in all cases, and was obviously hypocellular in four. In four cases, in which the urinary excretion of labelled vitamin B_{12} was less than 15 per cent., the test of vitamin-B_{12} absorption was repeated after treatment with thyroxine for five to 12 months, when the patients were in good health. In three cases the urinary excretion of the labelled vitamin was similar to the value obtained before treatment, but in one (Case 8) the excretion was considerably greater after treatment (Table VIII).

In the present investigation no control series of normal subjects was studied. Direct comparison with published results in normal subjects can be made only when the same technique has been employed, and the same dose of labelled vitamin B_{12} given, as in the present study. It is known that in normal subjects the amount of vitamin B_{12} absorbed increases in relation to the oral dose up to about 1·0 μg. When the amount given is increased further, the absolute amount of vitamin B_{12} absorbed is no greater than after the dose of 1 μg., so that with oral doses of greater than this amount the proportion becomes smaller (Glass, Boyd, and Stephanson, 1954; Baker and Mollin, 1955; Callender and Evans, 1955*b*). Normal control subjects were found by Callender and Evans (1955*a*) to excrete 15·8 to 39·6 per cent. of the oral dose in the urine in 24 hours. A wider range (6·2 to 33·4 per cent.) was reported by Goldberg, Trivedi, and Oliner (1957)

TABLE VIII

Haematological and other Relevant Details, and Results of Vitamin-B_{12} Absorption Tests, in 20 Cases of Hypothyroidism

	Peripheral blood							*Vitamin-B_{12} urinary excretion test (%/24 hrs.)*			
									When hypothyroid		*When euthyroid*
Case number	*Haemoglobin (g./100 ml.)*	*Red cells (mill./cu. mm.)*	*Colour index*	*Bone marrow*	*Gastric acidity*	*Serum iron (μg./100 ml.)*	*Serum vitamin B_{12} (μμg./ml.)*	*Gastric mucosa*	*Without intrinsic factor*	*With intrinsic factor*	*Without intrinsic factor*
1	14·3	4·5	1·1	Normoblastic	Normal	105	560	..	19·9	..	..
2	13·3	4·5	1·0	„ , hypocellular	H.F.A.	115	..	Normal	11·1	10·2	12·6
3	13·5	4·1	1·1	„ „	„	..	..	..	11·0	18·3	9·9
5	13·8	4·5	1·0	..	..	..	280	..	15·3	18·6	..
6	13·9	4·3	1·1	Normoblastic	H.F.A.	112	220	Gastritis	16·5	..	..
7	14·1	4·5	1·1	„	Normal	..	220	..	11·2	..	12·3
8	13·6	5·0	0·9	„	„	110	230	..	13·9	10·3	23·8
9	13·5	4·4	1·0	„	„	..	..	Gastritis	15·8	24·0	..
18	9·6	3·6	0·9	„	..	35	180	..	10·6	..	..
19	11·0	4·1	0·9	„ , hypocellular	Normal	65	..	..	20·0	23·0	..
20	12·9	4·1	1·1	„ „	„	77	230	..	15·7	20·8	..
22	12·4	4·2	1·0	..	H.F.A.	62	180	..	31·0	..	..
23	14·3	3·1	1·5	Megaloblastic	„	130	40	Atrophy	0·6	8·5	0·5
24	10·6	2·4	1·5	„	„	..	5	..	0·5	13·8	3·6
25	9·3	2·9	1·1	„	„	..	15	Gastritis	0·0	11·5	..
26	8·6	1·7	1·7	„	„	..	20	..	3·0	19·8	3·2
27	14·1	4·3	1·1	*	„	..	..	..	0·0	14·0	..
28	12·4	3·3	1·3	*	„	95	..	..	0·5	20·6	..
29	14·7	5·0	1·0	Normoblastic	„	..	100	Atrophy	0·8	9·2	1·8
30	10·9	2·5	1·5	Megaloblastic	„	106	..	Atrophy	0·4	6·7	..

* Cases 27 and 28. Erythropoiesis had been megaloblastic before starting treatment with vitamin B_{12}.
H.F.A. = histamine-fast achlorhydria.

in haematologically normal subjects. Using a smaller dose of labelled vitamin B_{12} than in the present study, Frost, Goldwein, and Kaufman (1957) found 10 to 38 per cent. of the oral dose in the urine in 24 hours in normal subjects. From consideration of published results, we regarded excretion of more than 10 per cent. of the oral dose in the urine in 24 hours as within the normal range. In interpreting the results of the test it is inferred that urinary excretion of the labelled vitamin is an index of absorption. Callender and Evans (1955*a*) found that this was a valid assumption, and estimated that the average urinary excretion was approximately one-third of the amount of labelled vitamin B_{12} absorbed.

Hypothyroidism with vitamin-B_{12} deficiency. In eight patients (Cases 23 to 30, Table VIII) the 24-hour urinary excretion of labelled vitamin B_{12}, following an oral dose given without added intrinsic factor, was 3 per cent. or less, and in seven of these it was less than 1 per cent. When intrinsic factor (100 mg.) was given along with the oral dose, the urinary excretion was greatly increased in all cases. In four patients the urinary excretion test was repeated three to eight months later, when the patient had been treated with thyroxine and appeared to be euthyroid. Although there was a slight increase in the amount of radioactivity in the urine in two cases, the 24-hour urinary excretion of labelled vitamin B_{12} was still less than 4 per cent. of the oral dose. In these eight cases the results of the urinary excretion test, with and without intrinsic factor, are typical of the values obtained in pernicious anaemia (Callender and Evans, 1955*a*; Mollin and Baker, 1955; Goldberg, Trivedi, and Oliner, 1957; Frost, Goldwein, and Kaufman, 1957), and it appears that the impaired absorption of vitamin B_{12} resulted from deficiency of intrinsic-factor activity. In the four cases in which further tests were done, this deficiency of intrinsic factor was not corrected after adequate treatment of the hypothyroidism with thyroxine.

Two of these patients (Cases 27 and 28) were already known to have pernicious anaemia at the time of diagnosis of hypothyroidism, and had been treated with apparently adequate dosage of vitamin B_{12} or liver extract for seven and 12 years respectively. Five (Cases 23 to 26 and 30) were found to have macrocytic anaemia, megaloblastic erythropoiesis, and histamine-fast achlorhydria. The serum level of vitamin B_{12} was estimated in four of these five cases, and was abnormally low, in the range associated with pernicious anaemia (Spray and Witts, 1958). In two there was gross atrophy of the gastric mucosa, but in one (Case 25) there was no atrophy, and some oxyntic cells were seen. These five patients all showed a prompt and adequate haematological response to treatment with vitamin B_{12}. There seems little doubt that these five patients, and also the two already mentioned (Cases 27 and 28), were suffering from true Addisonian pernicious anaemia in addition to hypothyroidism.

Case 29 is of particular interest. This patient had hypothyroidism associated with Hashimoto's disease of the thyroid. The results of the vitamin-B_{12} absorption tests were typical of pernicious anaemia; histamine-fast achlorhydria was present, there was atrophy of the gastric mucosa (Plate 42, Fig. 9), and the level of serum vitamin B_{12} was below the normal range, although not so low as

in Cases 24 to 26 and 30. Nevertheless the marrow showed normoblastic erythropoiesis, and the peripheral blood was normal. It seems probable that this patient will ultimately develop pernicious anaemia, but at the time of study the body stores of vitamin B_{12} had not yet fallen sufficiently low to result in abnormalities of the marrow and peripheral blood.

Discussion

Anaemia is commonly regarded as a frequent complication of hypothyroidism. In many of the early reports the depressed thyroid function was regarded as the sole cause of the anaemia, though it was frequently observed that the response to treatment with thyroid alone was slow. In contrast to the cutaneous changes and swelling, which disappeared within a few weeks, the anaemia often persisted for months (Means, 1948). Many different types of blood picture have been described, and this lack of uniformity is difficult to reconcile with a single factor (Leonard, Falconer, and Ellenhorn, 1951). In our patients anaemia was rare in the absence of either iron or vitamin-B_{12} deficiency, and in 79 out of 84 patients with normocytic blood films the haemoglobin was within previously reported ranges of normal values (Wintrobe, 1933; Osgood, 1935; Berry, Cowin, and Magee, 1952). In some of the earlier accounts of the coexistence of anaemia and myxoedema the haemoglobin concentration was not greatly depressed, and not outside the range which is now accepted as normal (Emery, 1923). The numerous reports describing anaemia in hypothyroidism usually do not state the incidence of the association. Means (1948) reported that in about half the cases of myxoedema the haemoglobin was under 70 per cent. Hypothyroidism is now probably diagnosed at an earlier stage, and the shorter interval before diagnosis may militate against the development of anaemia and explain the lower incidence in the present series. This may particularly apply to patients developing hypothyroidism after ^{131}I therapy, since they report regularly at hospital. The haemoglobin levels found, however, were not lower in patients with spontaneous myxoedema, in whom the diagnosis was more delayed. Furthermore, in the patients with anaemia there was no evidence that either the duration or the severity of the hypothyroidism was exceptional. Larsson (1957) made a similar observation.

The anaemia commonly associated with myxoedema is macrocytic (Bomford, 1938; Holbøll, 1943; Decourt, Guillemin, and Michard, 1949; Leonard, Falconer, and Ellenhorn, 1951). In the present study, however, macrocytosis of sufficient degree to be recognizable on careful inspection of blood films was not seen in uncomplicated cases, and when it was evident there was some explanation other than hypothyroidism for its presence. No detailed investigation of cell size using Price–Jones curves was carried out, and it is clearly impossible to detect a slight uniform increase in cell size by examination of blood films alone. In some cases a decrease in mean corpuscular volume was noted on treatment with thyroxine. Clearly our results are not incompatible with the earlier descriptions of an increase in cell size in myxoedema; but the survey

indicates that if macrocytosis is seen in the blood films, or a severe degree of anaemia is present, some cause in addition to the hypothyroidism can generally be detected by modern haematological methods.

In contrast to the evidence regarding the incidence of anaemia, there is general agreement regarding changes in blood volume. Several workers have found that the plasma and total blood volumes are reduced in myxoedema, and in most studies there has been a significant increase after treatment of the hypothyroidism (Thompson, 1926; Rowntree, Brown, and Roth, 1929; Blumgart, Gargill, and Gilligan, 1931; Gibson and Harris, 1939). Muldowney, Crooks, and Wayne (1957) found that the red-cell volume, deduced indirectly from the plasma volume and venous haematocrit, was consistently below normal in hypothyroidism and increased significantly after treatment. Direct measurement of total red-cell volume by ^{51}Cr showed an increase after treatment of the hypothyroidism in five of six cases in the present study. The results reported here showed that in some cases of hypothyroidism the plasma volume also increased after treatment, so that the haemoglobin level did not change. In other cases, however, the haemoglobin increased after treatment with thyroxine, and the plasma volume did not change significantly. The explanation of these different patterns of behaviour of the plasma volume in hypothyroidism is not at present clear.

After the experimental production of hypothyroidism in animals, the bone marrow becomes hypoplastic (Tatum, 1913; Kunde, Green, and Burns, 1932; Gordon, Kadow, Finkelstein, and Charipper, 1946; Adam and Doljanski, 1958). Hypoplasia of all types of marrow cells has also been reported in hypothyroidism in man (Jones, 1940; Axelrod and Berman, 1951). In the present study the marrow was hypocellular and normoblastic in four of 10 cases in which there was no evidence of deficiency of iron or vitamin B_{12}. The reduction in total red-cell volume, with hypocellularity of the erythropoietic cells, is in accord with the hypothesis of Bomford (1938), that in hypothyroidism there is a reduction in the total mass of red cells and their precursors, resulting from reduced oxygen consumption in the tissues. Muldowney, Crooks, and Wayne (1957) supported this hypothesis, and provided further evidence in favour of it by showing that the total red-cell volume became greater with the increased oxygen consumption produced by the administration of dinitrophenol, without increase in thyroid activity. The finding of normal red-cell survival is in agreement with most reports (Rodnan and Jensen, 1957; McClellan, Donegan, Thorup, and Leavell, 1958), and does not confirm the apparent reduction in red-cell life-span in myxoedema described by Buso, Olavarrieta, and Suarez (1958).

The association of pernicious anaemia and hypothyroidism has been previously reported (Bomford, 1938; Vanotti, 1940; Schneiderbauer, 1941; Means, 1948; Gilbert-Dreyfus and Mamou, 1949; Deane and Currence, 1950; Leonard, Falconer, and Ellenhorn, 1951; Bousser and de Menibus, 1952; Castle and Wallerstein, 1955; Wintrobe, 1956). Daughaday, Williams, and Daland (1948) considered that Addisonian macrocytic anaemia was rare in hypothyroidism, but five patients with both conditions were described by Means, Lerman, and

Castle (1930). Three out of 48 patients with myxoedema described by Larsson (1957) also had pernicious anaemia, and he considered that the association of the two conditions was not uncommon. Wilkinson (1933) found three cases of myxoedema in 370 cases of pernicious anaemia, and Murphy and Howard (1936) five cases out of 440. It is possible that cases of coincidence of the two conditions may have been overlooked in the past. Many symptoms, such as tiredness, weakness, pallor, sensitivity to cold, are common to pernicious anaemia and myxoedema. As Castle and Wallerstein (1955) pointed out, when the pernicious anaemia is adequately treated the clinical and haematological improvement may be so great that the coexisting hypothyroidism may be overlooked. Furthermore, the basal metabolic rate tends to be elevated in some cases of pernicious anaemia (Suzman, 1932), and this may make the diagnosis of associated hypothyroidism more difficult. Study of the case reports of coexisting myxoedema and pernicious anaemia shows that the true nature of the anaemia may not be readily apparent (Greene, 1936; Leonard, Falconer, and Ellenhorn, 1951). Achlorhydria was frequently present in our hypothyroid patients, and Lerman and Means (1932) found that 53 per cent. of their patients with myxoedema had complete achlorhydria. Greene (1936) noted achlorhydria in five of 14 cases of myxoedema. The findings in our own Case 29, and the reported association of the two conditions, certainly suggest that hypothyroid patients showing achlorhydria should be fully investigated for evidence of vitamin-B_{12} deficiency. It has been suggested that defective gastric secretion and loss of appetite resulting from myxoedema might lead to the development of vitamin-B_{12} deficiency and subsequent megaloblastic anaemia (Wintrobe, 1956). Considering the very varied time relationships in the development of the two disorders, that mechanism could be responsible for only a few of the cases in which pernicious anaemia and myxoedema occur in the same patient.

The response to specific treatment in pernicious anaemia may be incomplete when hypothyroidism is present as well (Deane and Currence, 1950; Wintrobe, 1956; Bousser and de Menibus, 1952; Whitby and Britton, 1953; Castle and Wallerstein, 1955). This effect was observed in one patient in the present study; but in one other patient, who developed myxoedema while receiving treatment for pernicious anaemia, the blood remained normal in spite of undoubted hypothyroidism, and in three patients, with both disorders untreated, the blood returned to normal with vitamin-B_{12} therapy alone, before thyroxine was administered. These results show that, although the response to vitamin-B_{12} therapy in pernicious anaemia may be impaired by coexisting hypothyroidism, this effect cannot always be demonstrated. A satisfactory haematological response in a patient with pernicious anaemia does not by itself exclude the possibility of coexisting hypothyroidism.

Leithold, David, and Best (1958) reported that in three out of seven cases of myxoedema there was severe impairment of absorption of vitamin B_{12}, which was not improved when intrinsic factor was given with the labelled B_{12}, and they suggested that in some cases of hypothyroidism there is an intestinal block in the absorption of vitamin B_{12}. In all our patients shown to have vitamin-B_{12}

deficiency absorption was increased by the administration of intrinsic factor. This included the one patient who showed all the features of pernicious anaemia except the changes in the marrow and blood. In all the other patients with hypothyroidism, who did not have pernicious anaemia, the results of the tests of vitamin-B_{12} absorption were normal, but in approximately half of these cases the value obtained was at the lower border of the normal range. In three of the four cases studied again after treatment with thyroxine for several months, the absorption of vitamin B_{12}, as measured by the urinary excretion test, was still at the lower extreme of the normal range. When the patients with pernicious anaemia were studied again after treatment with vitamin B_{12} and with thyroxine, the results of the tests of vitamin-B_{12} absorption were still typical of those found in pernicious anaemia.

The reason for the association of hypothyroidism and pernicious anaemia is not clear. It is now recognized that most cases of idiopathic hypothyroidism are probably associated with an auto-immune mechanism (Owen and Smart, 1958). The cause of pernicious anaemia is still obscure, but recent studies have suggested that an auto-immune process may be important (Taylor, 1959). There is a familial incidence of both conditions (Bartels, 1941; Neele, 1947; Callender and Denborough, 1957). In cases where they coexist, the time relationships suggest that the hypothyroidism and pernicious anaemia develop independently. The results of the present investigation have shown that deficiency of thyroid hormone, by itself, does not lead to vitamin-B_{12} deficiency. It is apparent from this study that, if macrocytosis is observed in the blood film of a patient with hypothyroidism, it should not be accepted as due to the anaemia of myxoedema without full investigation to exclude an associated vitamin-B_{12} deficiency.

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Summary

The incidence of anaemia has been investigated in a series of 166 cases of hypothyroidism. The hypothyroidism was either idiopathic or consequent on radiation therapy or surgery. Of 116 patients in whom the blood was examined before treatment, the red cells appeared normocytic in 84 (72 per cent.); 79 of these patients were not anaemic.

A mild normocytic anaemia was present in five patients in whom there was no evidence of a cause of anaemia other than hypothyroidism; in these cases the haemoglobin increased to normal during treatment with thyroxine alone.

The red-cell volume increased after treatment in five out of six cases of hypothyroidism. In three cases in which the haemoglobin level increased considerably after treatment, the red-cell volume increased but the plasma volume showed no significant change. In two patients without anaemia, in whom the haemoglobin level was unchanged after treatment, both red-cell volume and plasma volume increased.

The survival of red cells was normal in eight cases, and the utilization of a tracer dose of radio-iron normal in three cases, of hypothyroidism.

Iron-deficiency anaemia was present in 17 cases. This form of anaemia was not influenced by thyroxine therapy, and responded adequately to iron without treatment of the hypothyroidism.

There was a high incidence of pernicious anaemia in this series of cases of hypothyroidism, the two conditions occurring together in 13 patients (7·8 per cent.). In addition there was one patient with gastric atrophy, defective vitamin-B_{12} absorption, and a low level of vitamin B_{12} in the serum, who had not yet developed megaloblastic anaemia. The incidence was greatest (10·3 per cent.) in the patients with idiopathic hypothyroidism. Hypothyroidism alone did not depress vitamin-B_{12} absorption, and the two conditions developed independently. The reason for their association is not known, but macrocytic anaemia apart from pernicious anaemia was rare. If macrocytosis is detected in the blood film of a myxoedematous patient, it is important not to regard this as due to hypothyroidism without first excluding vitamin-B_{12} deficiency.

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FIG. 7 Case 23. Gastric mucosa, showing atrophy (×120)

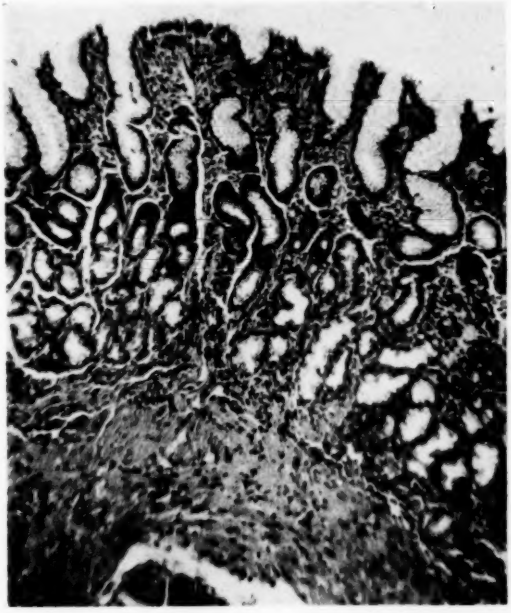

FIG. 8. Case 25. Gastric mucosa, showing moderate inflammatory infiltration, but absence of atrophy. A few oxyntic cells are present (×120)

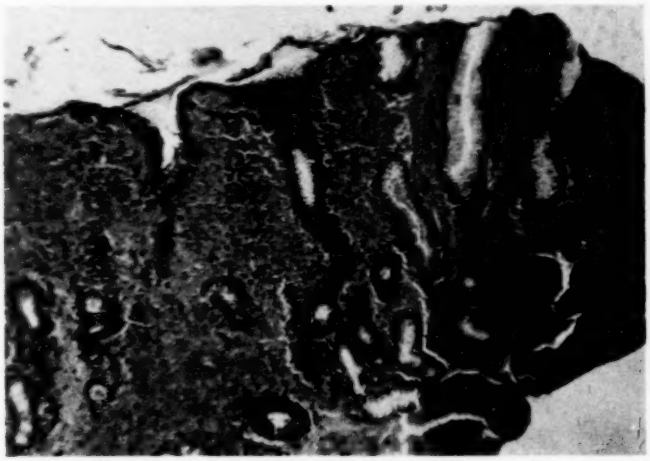

FIG. 9. Case 29. Gastric mucosa, showing atrophy (×120)

616.24–002.71

THE NATURAL HISTORY OF PULMONARY SARCOIDOSIS[1]

By HUGH SMELLIE and CLIFFORD HOYLE

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With Plates 43 to 47

Although some of the first accounts of sarcoidosis pointed out that the lungs might be affected, there are few early records, and fewer still referring to the natural history of this form. None of them deals with more than a few patients, rarely followed for long. They are thus both unrepresentative and incomplete. Most of what is yet known of the subject is in papers from the last decade, summarized in Table I with our findings for comparison. The reported outcome varies remarkably, improvement ranging from 29 per cent. (Siltzbach, 1955) to 83 per cent. (Löfgren, 1953), and mortality from 23 per cent. (Riley, 1950) to nil (Reisner, 1944; Löfgren, 1953). Such discrepancies might suggest either fundamental differences in the types of disease included, or more than one aetiology for sarcoidosis. There are, however, other reasons for them. One is the way in which the series were formed. Löfgren (1953) dealt with early sarcoidosis, others (for example Riley, 1950) with more advanced or even terminal disease. Many of Löfgren's patients (111 in 201) were found to have hilar lymph-node enlargement at an attack of erythema nodosum. As this form is much commoner in Sweden than it is here or in North America and, as Löfgren showed, is followed by a better prognosis, the favourable outcome in his patients cannot be applied to the run of the disorder elsewhere without reservation. Other series have been collected retrospectively from hospital records (Riley, 1950; Longcope and Freiman, 1952; Nitter, 1953; Cowdell, 1954), which in part accounts for their less favourable figures. Moreover, American papers include a high proportion of Negroes, ranging from 50 in 123 in Siltzbach's series (1955) to 42 in 50 in Riley's series (1950). As the American Negro often has a more florid form of sarcoidosis than the white European, his prognosis is probably worse, though figures are not conclusive.

A source of difficulty in assessing some recent papers is that they have included patients treated with corticosteroids in studies of the natural history. Siltzbach (1955) treated 26 of his 123 patients, but did not give a separate account of their progress, and Sones and Israel (1958) included 90 treated patients among 209. The only other recent paper (Scadding, 1956) did not mention whether any treated patients were included. Although the effect of steroid treatment upon the eventual outcome is not yet known, there is ample

[1] Received October 14, 1959.

evidence of almost uniform improvement in the appearance of the lung lesions, which conveys a biased view of the prognosis. A final obstacle to determining the natural course of pulmonary sarcoidosis is the difficulty of observing enough patients frequently and for a long time. Forty-nine of Siltzbach's (1955) 123 patients were followed for less than a year, with a minimum period of one month. Some authors have not given their range of observation (Reisner, 1944; Riley, 1950). On the other hand, Löfgren (1953) followed 201 patients, and Scadding (1956) 101, for at least two years.

TABLE I

Radiographic Course of Patients with Pulmonary Sarcoidosis

Author	*Year*	*Number of patients**	*Improved*	*No change*	*Deteriorated*	*Dead of sarcoid*	*Percentage improved*	*Percentage dead*
Reisner	1944	27	13	5	9	0	50	0
Riley	1950	44	17	5	12	10	39	23
Longcope and Freiman	1952	69	29		30	10	42	14
Löfgren	1953	201	167	0	34	0	83	0
Nitter	1953	90	36	7	34	12	41	13·5
Cowdell	1954	40	18	6	11	5	45	12·5
Siltzbach	1955	123	36	61	39	6	29	5
Scadding	1956	101	47	7	42	5	47	5
Sones and Israel	1958	209	..	..	..	16	76	7·6
Present series†	..	77	47	9	17	5	61	6

* The figures in this column refer to the number of patients for whom follow-up data were available.
† Untreated patients only.

Patients Investigated and Methods

Our experience of the natural history is based upon 125 of 213 patients with pulmonary sarcoidosis who were closely observed for more than two years from its discovery. With few exceptions they were in the care of one of the authors (C. H.). They came from various sources—from mass radiography clinics, from the ophthalmic and dermatological and other medical clinics of King's College Hospital, from general practitioners, and from colleagues at other hospitals—so that we believe they represent a cross-section of the sarcoid population. They were admitted to hospital initially for investigation, which followed the pattern described in earlier papers (Hoyle, Dawson, and Mather, 1954; Mather, Dawson, and Hoyle, 1955; Smellie and Hoyle, 1957). Special attention was given to any means of dating the onset, including previous radiographs and mass radiography films, which were seen whenever possible. Full clinical examination included search for any extrapulmonary sarcoidosis, with slit-lamp examination of the eyes. Fig. 1 shows the age at discovery of the disease in our 125 patients. Most of them were in the third and fourth decades. Female exceeded male patients in the ratio of 79 to 46. All were Europeans: there were no Negroes. Four gave a family history of sarcoidosis.

Postero-anterior and lateral chest radiographs at six feet were supplemented by hilar tomograms and fluoroscopy, and when necessary by bronchograms. Skin sensitivity to tuberculin followed the usual pattern (Hoyle, Dawson, and Mather, 1954). Routine cultures were made of sputum or gastric washings, and of morning urine, for *Mycobacterium tuberculosis*, and this organism was

isolated from five patients. One of these patients had progressive pulmonary tuberculosis as a terminal complication of sarcoidosis, confirmed at necropsy; the others have been included because their disorder conformed in other ways with sarcoidosis, and *M. tuberculosis* was grown on culture from each of them on one occasion only, despite many attempts. Histological support for the diagnosis of sarcoidosis was sought when available from biopsy of skin lesions,

FIG. 1. Pulmonary sarcoidosis. Age at discovery and sex in 125 patients.

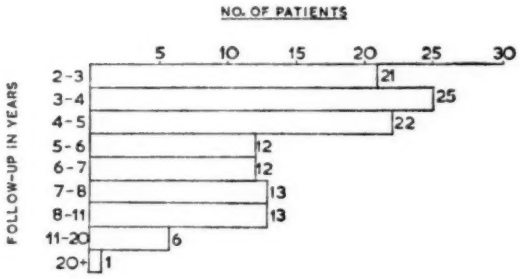

FIG. 2. Pulmonary sarcoid[illegible]. Duration of observation of 125 patients.

peripheral lymph-nodes, and conjunctiva (Crick, Hoyle, and Mather, 1955), or from the liver (Mather, Dawson, and Hoyle, 1955), and occasionally from the lung. It was found in 87 of the 125 patients. Biopsy was not attempted in 12 patients for various reasons, and liver or conjunctival biopsy specimens were negative in 26. These patients have been included because the diagnosis was not in doubt, and because their exclusion would have biased our evidence on the course of the disease. They are probably a group in which sarcoidosis is less florid than in patients with lesions readily accessible to biopsy. After investigation most patients attended a special clinic regularly. They have been observed for variable times, ranging from two to 22 years, half of them for more than four years (Fig. 2).

Results

Initial clinical features. Table II shows how the disorder was discovered, pulmonary lesions being present at the time in every case. There are several points for comment. A large number of patients (84 in 125) either were without symptoms, and were found by routine radiography (58), or had minor symptoms not attributable to sarcoidosis (26). Among the 41 who had clinical features

TABLE II

Mode of Discovery of Pulmonary Sarcoidosis in 125 Patients

By routine radiography		58
By investigation of symptoms referable to sarcoidosis:		41
Uveitis	18	
Erythema nodosum	12	
Skin sarcoids	5	
Lymphadenopathy	4	
Parotitis	1	
Polyarthritis	1	
By investigation of other symptoms (e. g. cough, chest pain, malaise)		26
Total		125

TABLE III

Extrapulmonary Lesions in 90 Patients

Ocular sarcoidosis	53
Peripheral lymphadenopathy	38
Splenomegaly	28
Skin sarcoids	17
Bone sarcoidosis (X-ray)	10
Cranial nerve palsy	4
Salivary gland enlargement	5
Hypercalcaemia	3

due to sarcoidosis the commonest findings were uveitis and erythema nodosum, the only ones of much value as signposts to the disorder at this stage. Skin sarcoids, enlarged peripheral lymph-nodes, parotid gland enlargement, and polyarthritis, though still regarded as classic features of sarcoidosis, were all much rarer both at the onset and later (Table III). In contrast with Löfgren's (1953) figure of 111 in 201, only 12 of our 125 patients were found to have sarcoidosis because of an attack of erythema nodosum; three others had erythema nodosum within the 12 months preceding discovery of their sarcoidosis, and one five months after an attack of sarcoid uveitis; a total of 16 patients in whom it was an early sign. Three more gave a history of erythema nodosum several years before their sarcoidosis was discovered. It was probably unrelated in two of them, and certainly in the other, whom we investigated fully at the time without finding any evidence of the cause, though she developed hilar lymph-node sarcoidosis seven years later.

Extrapulmonary sarcoidosis. Apart from erythema nodosum, 90 of the 125 patients had clinical evidence of extrapulmonary sarcoidosis at some time (Table III). As at the onset, the important feature was the frequency of ocular sarcoidosis (53 in 125; 42 per cent.), mainly uveitis, kerato-conjunctivitis sicca,

and conjunctival follicles (Crick, Hoyle, and Smellie, 1960). Peripheral lymphadenopathy and splenomegaly were again less frequent, and skin sarcoids less common than these (17 in 125; 14 per cent.). Bone lesions were found in 10 patients (8 per cent.), but facial palsy, salivary gland enlargement, and hypercalcaemia in a few only. None had clinical evidence of cardiac or alimentary tract sarcoidosis, or of lesions in the central nervous system apart from facial palsy.

TABLE IV

The Course of Extrapulmonary Sarcoidosis in 61 Patients related to the Course of their Pulmonary Lesions

Pulmonary radiographic course	*Number of patients*	*Extrapulmonary lesions*		
		Regressed	*Partially regressed*	*Persisted*
Clear	24	20	0	4 *
Improved	9	7	1	1 *
Unchanged	8	4	1	3
Worse	20	8	0	12
Total	61	39	2	20

* Ocular lesions only.

TABLE V

Relation of Extent of Extrapulmonary Sarcoidosis in 54 Patients to the Course of their Pulmonary Lesions

Number of extrapulmonary lesions	*Number improved*	*Number unchanged or worse*	*Total*
0	11	5	16
1	10	9	19
2	5	5	10
3	1	2	3
4	0	5	5
5	0	1	1
Total	27	27	54

($\chi^2 = 7{\cdot}648$; $n = 3$; $0{\cdot}1 > P > 0{\cdot}05$)

The course of the extrapulmonary lesions in 61 patients is recorded in Table IV, where it is related to that of their lesions in the lungs. On the whole they behave similarly, with the exception of uveitis, which may persist or recur after lung lesions have become quiescent or have cleared radiographically. Table V shows the relationship between the number of sites of extrapulmonary involvement and the course of the pulmonary lesions in 54 patients with infiltration in the lungs who were untreated. The trend is towards a worse prognosis for those with more extrapulmonary lesions, but the difference falls just short of significance.

Clinical course of pulmonary sarcoidosis. There were few symptoms and no abnormal physical signs attributable to early pulmonary sarcoidosis—that is, at the onset and before remission or progression to pulmonary fibrosis.[2] When

[2] We have used the term 'pulmonary fibrosis' for linear shadows with lung distortion seen radiographically. Other types of shadow may also represent fibrotic lesions, but in these the presence of fibrosis cannot be deduced from the radiograph.

the lung lesions persisted, however, there was a gradual evolution of both symptoms and signs (Table VI). Dyspnoea, the main symptom, was a complaint at some time of 54 patients. The timing of its onset is related to the stage of the disease in Table VII. Patients with dyspnoea were divisible into two groups: those who had it at the onset, and those who developed it during the course of the disease. The first group (35 patients) all had early pulmonary

TABLE VI

Clinical Features in 125 Patients

Dyspnoea		54
Cough		46
Sputum (12 with pulmonary fibrosis)		23
Bronchiectasis		6
Finger clubbing		8
Haemoptysis		5
Bronchostenosis		4
Cor pulmonale	(5 fatal)	6
Spontaneous pneumothorax	(1 fatal)	5

TABLE VII

Analysis of Dyspnoea in 54 Patients

A. Onset of dyspnoea

1. Present at discovery:
   Increased in 4 only, who developed pulmonary fibrosis 35/54
2. After discovery:
   Mean time of onset, 5 years; range, 1–18 years. Coincided with pulmonary fibrosis in 14/19 19/54

B. Relation to chest radiograph

Radiographic appearance	*Number of patients**	*Grade of dyspnoea*		
		Slight	*Moderate*	*Severe*
Enlarged hilar nodes only	6/27	6	0	0
Pulmonary infiltration	27/73	25	1	1
Pulmonary fibrosis	21/25	10	7	4

Dyspnoea was regarded as slight when out of proportion to the patient's age and training on fairly strenuous exercise, such as running for a bus; as moderate when induced by such efforts as walking up hills or two flights of stairs; and as severe when produced by walking on the level for short distances, e.g. 100 yards.

* Patients have been classified according to their latest chest radiograph if the appearances have advanced, e.g. from nodal enlargement to infiltration or from infiltration to fibrosis. Otherwise they are classified according to their radiographic appearances at presentation. The denominators in this column refer to the numbers of patients whose disease was eventually classified in the respective categories. The numerators refer to the number in each category who complained of dyspnoea.

lesions, either enlarged hilar nodes with clear lung fields or pulmonary infiltration. Their dyspnoea was trivial, and worsened in only four, whose lesions eventually progressed to pulmonary fibrosis. Moreover, 23 of these 35 patients made no complaint of dyspnoea until their disease had been brought to light by a chance radiograph or by investigation for some non-respiratory symptom. In the second group (19 patients) dyspnoea appeared during the course of the disease, and was always attributable to progressive pulmonary sarcoidosis.

Moreover, 14 of these 19 noticed it about the time that pulmonary fibrosis appeared radiographically. Table VII also shows the relation between the radiographic appearance of the chest and the degree of dyspnoea. Moderate or severe dyspnoea was confined almost entirely to those with pulmonary fibrosis. Dyspnoea of any degree was rare with enlarged hilar nodes and normal lung fields, but was more frequent, though slight, with pulmonary infiltration.

Forty-six of our 125 patients complained of cough at some time; it was troublesome in 31, of whom 16 eventually had pulmonary fibrosis and seven had unchanged or increasing infiltration. Only four of these 31 patients eventually achieved a normal radiograph spontaneously. Twenty-three patients had sputum; it was purulent at times in 12, all of whom had radiographic evidence of advanced pulmonary sarcoidosis with fibrosis and bronchial distortion. Haemoptysis was rare, encountered in five patients only. Although four of them had advanced disease, their haemoptysis was trivial except in one patient, who was thought to have had a pulmonary infarct at the time, and who died after a further haemorrhage two years later.

Bronchial sarcoidosis was looked for by bronchoscopic biopsy whenever there was reason to anticipate gross structural changes. It was found in four patients. Two had stenosis of a single segmental bronchus, in the right and left upper lobes respectively, another of the right middle-lobe bronchus, and the fourth had stenosis of the bronchi leading to the middle lobe and apex of the lower lobe in the right lung. All four had cough, and one also had sputum due to secondary infection; all had radiographic evidence of collapse of the lobe or segment related to the bronchus involved. Bronchial biopsy in one patient showed typical non-caseating tubercle follicles beneath the bronchial mucosa. Biopsy in one other was negative. Bronchiectasis was found bronchographically in five out of 15 patients in whom it was suspected, and in one other at necropsy. All six showed the typical features, except that only three had finger clubbing. Gross pulmonary fibrosis was always evident radiographically, and the most severely bronchiectatic areas corresponded with the most fibrotic ones (Plate 43, Figs. 4 and 5). Thus bronchiectasis was always bilateral, involving mainly the upper lobes in two cases, mainly the lower lobes in two, and generalized in the remaining two.

Twenty-five patients had pulmonary fibrosis; eight of them had finger clubbing, and were the only ones in the series to show it. The rarity of clubbing contrasts with its frequency in severe pulmonary fibrosis due to some other causes. No reason could be found why eight of the patients with pulmonary fibrosis should have had clubbing, as opposed to the remainder who did not have it. Three of them had not shown any evidence of secondary bronchial infection. Nor were those with clubbing always the most advanced examples of fibrosis. One patient, known to have had generalized sarcoidosis for 17 years and pulmonary fibrosis with gross finger clubbing for at least six years, is still in good health apart from moderate dyspnoea on exertion.

Spontaneous pneumothorax as a complication of pulmonary sarcoidosis is now well recognized, but is rare apart from late fibrosis. Five of our 125 patients

have had a pneumothorax. Four had advanced fibrosis, two dying in the attack. At necropsy their pneumothoraces were associated with multiple bullae. One other patient has recently had a second attack, for which he required a thoracotomy after suction had failed to expand the lung or relieve extensive surgical emphysema. At operation he was found to have numerous bullae in a densely fibrotic upper lobe. One torn bulla was repaired, and the parietal pleura excised to assist pleurodesis. The lung expanded after further suction, and he made a satisfactory recovery.

TABLE VIII

Relationship between the Onset of Cor Pulmonale, the Duration of Disease, and Time of Death

Patient	*Interval between onset of cardiac failure from cor pulmonale, and death*	*Number of episodes of cardiac failure from cor pulmonale*	*Duration of sarcoidosis before first episode of cardiac failure from cor pulmonale*
D. E.	9 months	3	21 years
D. G.	10 months	2	3 years
E. H.	2½ years	4	13 years
L. K.	1 month	1	15 years
J. L.	At time of death	1	10 years
W. P.	6 months	2	9 years

All six patients in this series who had cor pulmonale have died, five of them from congestive heart failure. All six had clinical evidence of cor pulmonale, with right ventricular hypertrophy and cardiographic evidence, seen in tall spiked P waves and negative or low-voltage T waves in leads V1 to V3. The radiographic evidence was less convincing until cardiomegaly was advanced. Dilated pulmonary arteries, and enlargement of the outflow tract and the body of the right ventricle, were obscured in these patients by the fibrotic changes in the lungs. They were recognized eventually in five cases, although at necropsy they were found to be present in all six. Table VIII gives the time relationship of the onset of cor pulmonale to the duration of disease and the time of death. It shows clearly that the appearance of cardiac failure from cor pulmonale in sarcoidosis is terminal, and that survival for more than a year is unlikely. Also cor pulmonale is usually a late complication, arising between one and two decades from the discovery of sarcoidosis. The one exception, a young woman (D. G.) who died four years after the discovery of her sarcoidosis, had almost certainly had her disease for 12 years; she gave a history of iritis, which could have marked the true onset of her illness, eight years before her pulmonary lesions were found by mass radiography.

The clinical outcome in our 125 patients is summarized in Table IX. The remarkable lack of incapacitating symptoms is emphasized by the fact that 109 of the total group (87 per cent.) still pursue a normal life. Many of these patients have recovered completely after an onset of the disease with hilar node enlargement, which subsided, and was not followed by any other sarcoid features (see Table XIV). Others have had pulmonary infiltration which has either

cleared spontaneously or has left radiographic changes limited in severity or non-progressive, so that the course has not led to disablement. Additional to these groups is another comprising patients with quite severe pulmonary fibrosis, yet not sufficient to interfere with physical activities or to stop them from working. Here there is usually impairment of lung function on forced exercise, or detectable by physiological studies (Marshall, Smellie, Baylis, Hoyle, and Bates, 1958). Thus disablement from pulmonary sarcoidosis is

TABLE IX

Summary of Clinical Outcome in 125 Patients Followed for two Years or More

		Number of patients
1. Well and leading a normal life		109 (87 per cent.)
2. Disabled		4 (3 per cent.)
Lung failure or secondary infection	3	
Blindness	1	
Dead (mean survival 10 years: range 3–22 years)		12 (10 per cent.)
Cor pulmonale	5 (1 with pulmonary tuberculosis)	
Lung failure	2	
Spontaneous pneumothorax	1	
Haemoptysis	1	
Unrelated	3	

almost invariably due to steadily progressive disease with relentless fibrosis. In all, 12 of 125 patients have died, nine from sarcoidosis with severe pulmonary fibrosis, and three from unrelated causes. The mortality from sarcoidosis for untreated patients was 6 per cent. Cor pulmonale accounted for five deaths, and lung failure from fibrosis for the other four. Only one patient in this series developed caseous tuberculosis as a complication: it appeared late in the course of a progressively fibrotic pulmonary sarcoidosis, and she died from cor pulmonale 15 years after the discovery of hilar lymph-node enlargement. Necropsy confirmed the presence of active caseous tuberculosis, with cavities in both upper lobes, and of diffuse fibrotic sarcoidosis throughout the rest of both lungs (Hoyle, 1947).

Radiology of pulmonary sarcoidosis. Hilar node enlargement from sarcoidosis has a characteristic radiographic appearance, which we have described elsewhere (Smellie and Hoyle, 1957). But past descriptions of the pulmonary infiltration have not agreed on any uniform terminology, relying on terms such as 'miliary' often without adequate illustration. There is need of stricter definition. Table X gives the classification we have used, and the incidence of the various types of shadowing in 94 patients whose first radiographs we were able to use for this purpose. One further patient is not included because her sarcoidosis was complicated by hypogammaglobulinaemia and bronchiectasis. By far the commonest appearance (76 in 94) is of multiple small shadows for which the term 'nodular' is a suitable description. The size of individual nodules varies from patient to patient, but we have chosen 1 mm. diameter as an arbitrary lower limit. Fine and coarse nodular infiltration are readily distinguished by inspection; by measurement, fine nodular shadows range approximately from 1 mm. to 3 mm. in diameter (Plate 44, Fig. 6), and coarse ones from 3 mm. to 5 mm. (Plate 44, Fig. 7). This nodular infiltration is distinct from a

second form—fine stippling—composed of minute shadows uniform in size, and usually also in distribution, giving a 'ground-glass' appearance (Plate 44, Fig. 8) (eight in 94). Here the individual lesions are difficult to measure, as they are of pin-point size, less than 1 mm. in diameter. A striking but infrequent appearance due to sarcoidosis (Plate 45, Fig. 9) is of scattered large shadows due to patches of infiltration (five in 94). Five patients with bilateral hilar node enlargement also had isolated patchy shadows in both upper zones, similar to Ghon foci (Plate 45, Fig, 10), though they all had a negative tuberculin response, clinical and histological evidence of sarcoidosis, and negative bacteriological findings for *M. tuberculosis*.

TABLE X

Types of Pulmonary Infiltration, Excluding Fibrosis, seen in the First Available Chest Radiographs of 94 Patients with Sarcoidosis

Types of pulmonary infiltration	*Number of patients*
Scattered nodular shadows:	76
Fine (1 to 3 mm. in diameter) 50	
Coarse (3 to 5 mm. in diameter) 26	
Fine stippling (less than 1 mm. in diameter)	8
Scattered patches over 1 cm. in diameter	5
Localized upper-zone patches like Ghon foci	5
Total	94

TABLE XI

Bilateral Distribution of Pulmonary Shadows in 94 Patients with Pulmonary Infiltration

Diffusely scattered shadows . .	43
Mid-zone shadows mainly . .	39
Upper zone shadows mainly . .	10
Lower zone shadows mainly . .	2
Total	94

Upper zone = above a horizontal line drawn through the anterior ends of the second ribs.
Mid-zone = between upper and lower zones.
Lower zone = below a horizontal line drawn through the anterior ends of the fourth ribs.

We found that the pulmonary lesions almost invariably maintained their initial pattern throughout the course of the disease, until either spontaneous clearing occurred or their appearance became distorted by fibrosis. Their initial classification remained unaltered throughout, though nodular infiltration occasionally became coarser and, more rarely, finer. Extension of shadows into hitherto normal areas of lung was seldom seen. The distribution of pulmonary infiltration is given in Table XI, where the zonal classification is that in common use (Foster–Carter, Myers, Goddard, Young, and Benjamin, 1952). Forty-three patients had diffuse bilateral infiltration : 30 with nodular shadows, eight with

fine stippling, and five with scattered patchy shadows. Thirty-nine had lesions confined mainly to the mid-zones, all of the nodular type. Ten had upper zone lesions, in five cases nodular and in the others resembling primary tuberculous foci. Only two patients had nodular lesions mainly in the lower zones. Whatever the distribution, the apices of the lungs were rarely affected. All 94 patients had bilateral pulmonary lesions, and they were also symmetrical in all but 13.

Pulmonary fibrosis due to sacroidosis can be readily detected radiographically only when it is already gross. Even when moderately advanced it may be invisible (Plate 46, Fig, 11; Plate 47, Fig. 12). The earliest sign is the appearance of linear streaks, usually radiating into the lung fields from the hila, and adding a reticular appearance to the infiltration. Later, as fibrosis advances, the hilar

TABLE XII

Initial Chest Radiographs of 125 Patients

Enlarged hilar nodes only	48 (38 per cent.)
Pulmonary infiltration and enlarged hilar nodes	62 (50 per cent.)
Pulmonary infiltration only	9 (7 per cent.)
Pulmonary fibrosis	6 (5 per cent.)

shadows are distorted, and bullae or bronchiectasis give further evidence. Eventually the commonest appearance is of condensations of fibrous tissue around the elevated hila, spreading horizontally into the lower parts of the upper zones of both lungs, sparing the apices and lower lobes, which are over-inflated (18 in 25). Occasionally the mid- (6 in 25) and lower zones (1 in 25) are mainly involved. Condensation of the fibrous tissue may rarely lead to the formation of tumour-like opacities near the mediastinum. Pleural fibrosis with resulting thickening has not been seen in this series; it is rare in sarcoidosis because effusion is rare. When fibrosis is of very long standing it may be the sole remaining evidence of the disease, as in three of our patients. At necropsy no follicles could be found, though in each case the lungs were extensively destroyed by dense hyalinized fibrosis. But for preceding evidence it would have been impossible to tell that sarcoidosis was responsible.

Radiographic course. Table XII gives the details of the chest radiographs at the time of discovery of their sarcoidosis in our 125 patients. By far the commonest appearances were either hilar lymph-node enlargement with clear lung fields (48 in 125) or pulmonary infiltration with nodal enlargement (62 in 125). Pulmonary infiltration alone (nine in 125) was rare as an initial finding. So also was pulmonary fibrosis (six in 125), though it is important because of the difficulty in establishing the diagnosis at this late stage if there are no other sarcoid features.

In order to assess the natural course of pulmonary sarcoidosis it is necessary to select patients who are seen from an early stage of their disease and have not been treated. We have therefore excluded the six patients (Table XII) who already had advanced disease, with pulmonary fibrosis, at the time of discovery. Sixty others, with less advanced disease, were treated with antituberculous drugs or corticosteroids at some time, either for ocular sarcoidosis with impairment of vision, or because their pulmonary disease deteriorated. The remaining

59 patients were all followed from an early phase of the disorder, and were untreated. This group is biased by a high proportion of the less seriously affected patients. To reduce the error in estimating the natural course, we have included with them 18 of those who were treated because of deterioration after periods varying from two to 11 years. The mean duration of observation before treatment began was five years. In analysing the combined group of 77 patients,

TABLE XIII

Radiographic Course of Pulmonary Sarcoidosis in 77 Untreated Patients Followed for 2 Years or More

	Number of patients	*Time of appearance*		
		Mean		*Range*
Clear radiograph	39 (51 per cent.)	12·1	months	2–38
Lesions decreasing	8 (10 per cent.)			
Unchanged	9 (12 per cent.)			
Lesions increasing	11 (14 per cent.)			
Pulmonary fibrosis (5 dead)	10 (13 per cent.)	5·4	years	2–14
Total	77			

TABLE XIV

Radiographic Course of 41 Untreated Patients with Hilar Node Sarcoidosis Followed for Two Years or More

	Number of patients	*Time of appearance*		
		Mean		*Range*
Clear radiograph (via pulmonary infiltration in 8)	25 (61 per cent.)	10·3	months	2–31
Lesions regressing	4 (10 per cent.)			
Nodes unchanged	3 (7 per cent.)			
Infiltration increasing	6 (15 per cent.)			
Pulmonary fibrosis (2 dead)	3 (7 per cent.)	5·4	years	4–7
Total	41			

assessment of the follow-up is recorded as the outcome to date in those who were never treated, and the outcome at the start of treatment in the others. Of these 77 patients, 41 presented enlarged hilar lymph-nodes and clear lung fields, 30 enlarged hilar lymph-nodes and pulmonary infiltration, and six pulmonary infiltration alone. Table XIII shows their radiographic course. Forty-seven (61 per cent.) improved, 39 (51 per cent.) achieving normal radiographs in a mean time of one year from discovery. Twenty-one (27 per cent.) deteriorated, and in 10 of these (13 per cent.) the disease advanced to pulmonary fibrosis in a mean time of 5·4 years. For patients who initially had hilar lymph-node enlargement and clear lung fields the outlook was better than for the group as a whole (Table XIV), nearly two-thirds (25 in 41) achieving normal radiographs in a mean time of just under one year. Eighteen of the 41 patients in this group developed pulmonary infiltration. It appeared usually within the first year of observation, and in 12 of these patients the size of the hilar nodes diminished simultaneously.

Eight had only transient infiltration, but it persisted in the other 10, three of whom now have pulmonary fibrosis, which appeared in about five years.

In all, 54 of the 77 patients had pulmonary infiltration, and its radiographic course is shown in Table XV. Eighteen were the patients, already mentioned, who presented hilar node enlargement and developed pulmonary infiltration subsequently; the other 36 had it when first seen. Twenty-two of these 54 patients achieved normal radiographs in a mean time of 14·5 months from discovery. Five others are still improving. Thus spontaneous clearing or improvement has occurred in half of this group. All but five of the 22 who achieved normal radiographs did so within two years of discovery, so that

TABLE XV

Radiographic Course of Pulmonary Infiltration in 54 Untreated Patients with Sarcoidosis Followed for Two Years or More

		Time of appearance		
	Number of patients	*Mean*		*Range*
Clear radiograph . . .	22 (41 per cent.)	14·5	months	2–38
Infiltration decreasing . .	5 (9 per cent.)			
Unchanged	6 (11 per cent.)			
Infiltration increasing (1 dead) .	11 (20 per cent.)			
Pulmonary fibrosis (5 dead) .	10 (19 per cent.)	5·4	years	2–14
Total	54			

patients whose pulmonary infiltration persists without improving for more than two years have small chance of achieving spontaneous clearing. Furthermore, of 27 patients whose pulmonary infiltration persisted for more than three years, none improved, and 21 (78 per cent.) deteriorated. Ten of these patients eventually were found to have pulmonary fibrosis radiographically, which appeared in a mean time of 5·4 years (range two to 14 years) from discovery of their disease. It is likely also that in time some of the others, in whom infiltration so far is unchanged or progressing, will develop pulmonary fibrosis, as they have as yet been observed for less time (mean four years) than those who already have fibrosis (nine years). Six of the 54 patients have died, five from pulmonary sarcoidosis. The mean time from diagnosis to death was 15 years (range eight to 22 years).

Prognosis. The course of the pulmonary lesions in the present series determined the prognosis; serious impairment of health, or death, were attributable solely to this factor, with the exception of two patients who had transient uraemia due to hypercalcaemia. The rate of improvement of untreated pulmonary lesions was 61 per cent., and the mortality 6 per cent. (Table I). An important problem is to determine what factors other than treatment decide the course and prognosis. We have been largely unable to forecast the outcome in our patients early in their disorder, though such knowledge would have put their long-term management on a much more secure footing. One factor of importance, however, was established by Löfgren (1953): the good prognosis of pulmonary sarcoidosis with erythema nodosum at its onset. He found persistent pulmonary sarcoidosis less often after erythema nodosum than after routine

discovery of the disorder, the difference of 19·3 per cent. exceeding the standard error by more than three times. Most of his patients in that investigation had hilar node enlargement only, and his figures showed a definite trend towards a favourable outlook for the whole of this group, even for patients who did not have erythema nodosum. Other writers have commented upon this feature (Nitter, 1953; Scadding, 1956; Smellie and Hoyle, 1957), and it is confirmed by our figures. In Table XVI we have analysed these figures statistically, along

TABLE XVI

	Patients with enlarged hilar nodes only			*Patients with pulmonary infiltration*		
	Improved	*Worse or unchanged*	*Total*	*Improved*	*Worse or unchanged*	*Total*
Löfgren (1953)	43	12	55	22	13	35
Present series	24	11	35	17	18	35
Total	67	23	90	39	31	70

$\chi^2 = 5{\cdot}36$; $0{\cdot}05 > P > 0{\cdot}02$

with Löfgren's series (1953), the only one with enough detail which is similar in composition to our own, apart from its high percentage of patients with erythema nodosum. To correct for this factor we have excluded from Table XVI all patients with erythema nodosum in both series. In this way a group with enlarged hilar nodes only is compared with a group with pulmonary infiltration. In neither series can the association between the type of disease and the outcome be considered statistically significant.[3] Both series, however, show the same trend, in that the rate of radiographic improvement is greater for patients presenting enlarged hilar nodes than for those presenting pulmonary infiltration. If the two series be regarded as one, the combined value of χ^2 suggests a significant relationship.

From this analysis it is evident that the problem of determining what factors influence prognosis applies with added force to patients with pulmonary infiltration. Half of our 54 untreated patients with early pulmonary infiltration (Table XV) improved, and the other half were either unchanged or worse. We have compared these two halves as regards age, sex, sensitivity to tuberculin, extent of extrapulmonary involvement, mode of presentation, and type of pulmonary shadows. The age at onset, sex, and degree of tuberculin sensitivity were similar in both groups. Extrapulmonary lesions were more widespread in patients in whom pulmonary infiltration failed to improve. Relation of the type of presentation to prognosis gave the impression that the disease had a more favourable outcome when it was discovered by routine radiography than when found by investigation of symptoms. Thirteen of the 27 patients with pulmonary infiltration who improved, and only seven who were unchanged or deteriorated, were found by routine radiography. On the other hand, of 17 who presented symptoms referable to sarcoidosis, only five improved, and 12 were

[3] Here and for other analyses we have not given the statistical data when the result indicated a trend but did not amount to mathematical proof.

unchanged or deteriorated. Nitter (1953) noted that spontaneous improvement of pulmonary lesions was much more frequent in patients with 'miliary' shadows in their lungs than in those with nodular shadows of 3 to 5 mm. diameter. A similar trend was found in the present series, but proved not to be significant.

Discussion

The incidence of pulmonary sarcoidosis in this country is not known. It was estimated from mass radiographic surveys in Swiss recruits (Schonholzer, 1947) as 12 per 100,000, and in United States recruits (Michael, 1956) as 2·1 per 100,000; but among Swedish civilians Löfgren (1957) found it more common, varying from three to 14 per 10,000; in Stockholm the incidence was three in 10,000 for men and five in 10,000 for women. The highest incidences were respectively nine and 11 in 10,000 at 25 to 29 years. There is also increasing evidence of the prevalence of pulmonary or hilar node lesions among patients with sarcoidosis. Longcope and Freiman (1952) found the lungs affected in 80·2 per cent. at the Johns Hopkins Hospital, and 71·4 per cent. at the Massachusetts General Hospital, while Siltzbach (1955) found the incidence 92 per cent., and Sones and Israel (1958) 95 per cent. These American figures are like ours: 213 (93 per cent.) of our 230 patients have shown hilar node or pulmonary involvement radiographically. The reported incidence at other sites is nowhere comparable with these figures, a fact which leaves little doubt that the pulmonary form of sarcoidosis is the usual one. Its silence as regards symptoms is an added reason for regarding it as commoner than is recognized. Mass radiographic surveys in Sweden have recently detected about one-quarter as many subjects with sarcoidosis as with tuberculosis (Wijkström, 1955).

Clinical evidence is too sparse, or too indefinite, for studying the evolution of pulmonary sarcoidosis till late in its course. The deception is emphasized by the fact that six of the nine clinical effects in Table VI were confined to patients with pulmonary fibrosis. Although the other effects—dyspnoea, cough, and sputum—were met earlier, their significance was questionable at the time. Moreover, studies of lung function (Marshall, Smellie, Baylis, Hoyle, and Bates, 1958) gave normal results in patients of the present series with hilar node enlargement only, or with recent pulmonary infiltration. When pulmonary infiltration was more than two years old, defects of compliance and diffusion were found; but even then complaint of troublesome dyspnoea was usually much further delayed. It appeared only when the pulmonary lesions steadily increased (Table VII), and coincided usually with the radiographic recognition of fibrosis. A few patients with fibrosis escape dyspnoea (four in 25) and remain well. We think their prognosis is better because their sarcoidosis ends its active course within the time required for early lesions to become fibrotic. The other clinical features were related similarly to advanced disease. Of 31 patients with persistent or recurrent cough, all but four had had their lesions for more than two years, and most of them much longer. Half of these patients had pulmonary fibrosis. Purulent sputum was met in only 12, all of whom had gross fibrosis,

and six bronchiectasis; four have died, and two are respiratory cripples. Bronchiectasis was bilateral because of the diffuse disease, but it may be confined to contracted upper lobes. Finger clubbing was unusual (eight cases in 125), and is unexplained, unless pulmonary fibrosis in all of them, and secondary infection in some, was responsible. Similar fibrosis, however, was seen in 17 other patients, many of whom had secondary infection, though none had finger clubbing. Four patients had stenosis of a segmental or lobar bronchus along with progressive disease in the lungs. Citron and Scadding (1957), who pointed out that bronchostenosis is rare in sarcoidosis, described three examples of their own and four from previous reports (Turiaf, Marland, Rose, and Sors, 1952; Siltzbach and Som, 1952; Grimminger, 1955; Brun and Viallier, 1950). Four more examples have been recorded since, two by Kalbian (1957) and two by Honey and Jepson (1957). All these patients coughed, and most of them had wheezing, faint stridor, and sputum. Biopsies have shown that the disease may often be detected in the bronchial mucosa, but it rarely leads to symptoms (Benedict and Castleman, 1941; Olsen, 1946; Jacob, 1949; Siltzbach and Som, 1952; Harvier, Turiaf, Claisse, and Rose, 1950; Löfgren, 1953; Turiaf and Brun, 1955; Cowdell, 1954; Grimminger, 1955; Kalbian, 1957).

A fatal outcome from pulmonary sarcoidosis is a late, indeed a very late event in its natural history, confined to patients with progressive disease and extensive fibrosis. Nine of 125 in the present series, 7·2 per cent., have died so far from their sarcoidosis, a mortality similar to that found by Sones and Israel (1958) (7·6 per cent. in 209 patients), by Siltzbach (1955), and by Scadding (1956) (5 per cent.). Higher figures, 12·5 per cent., 13·5 per cent., 14 per cent., and 23 per cent., were recorded by Cowdell (1954), Nitter, (1953), Longcope and Freiman (1952), and Riley (1950) respectively, though there are reasons, already discussed, for regarding them as exceptional. Cor pulmonale, the cause of death in five of our patients, and present in another who died from lung failure, is always a remote sequel. Rarely seen before the first decade of the disease, it is usually fatal within a year of the first episode of cardiac failure. It follows severe, widespread, and long-standing pulmonary fibrosis, and we have not seen it in any of our patients apart from this. Its pathogenesis is uncertain. Clinical evidence of pulmonary hypertension is uniform, and was confirmed by catheterization in one of our patients. Anoxia from impaired diffusing capacity has been thought partly responsible (Austrian, McClement, Renzetti, Donald, Riley, and Cournand, 1951; Riley, Riley, and Hill, 1952). Several authors have drawn attention to sarcoid follicles in the small vessels as a possible cause of enhanced resistance to pulmonary blood-flow (Schaumann, 1936; Hoyle, 1947; Mallory, 1948; and Marshall, Smellie, Baylis, Hoyle, and Bates, 1958), and such lesions are thought also to impair diffusing capacity by causing focal obstruction to perfusion. Whatever the exact mechanisms, the essential concomitant appears to be severe pulmonary fibrosis.

An important question for the interpretation of the course of pulmonary sarcoidosis is the reliability of radiography for revealing early or resolving lesions. Over half of our patients showed radiographic evidence of pulmonary infiltration

when their disease was discovered (Table XII), and all but nine of them had enlarged hilar nodes also. It is conceivable that the hilar nodes and the lungs are involved together at the onset, and that patients with nodal enlargement but clear lung fields have subradiographic lesions in the lungs. For good reasons there are no detailed studies correlating lung biopsies with the radiographic features. But one of our patients, with cervical lymph-node sarcoidosis and

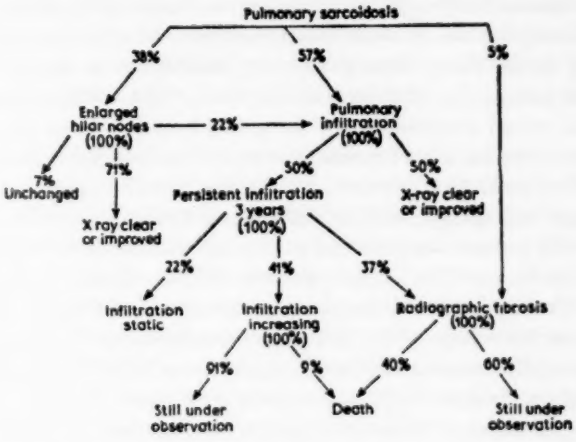

FIG. 3. The radiographic appearance of pulmonary sarcoidosis at discovery, and subsequent course in untreated patients.

unexplained dyspnoea for five years, had many small sarcoid follicles and fibrosis in a biopsy specimen from a lung (Plate 46, Fig. 11), although her lung fields were always radiographically normal. Another patient who had had diffuse pulmonary sarcoidosis which had cleared completely, leaving a normal radiograph, showed healed fibrotic lesions in a lung biopsy specimen taken at that time (Plate 47, Fig. 12). One other patient, in whom diffuse nodular infiltration became gradually less over 18 years, until she had an almost normal radiograph except in the right lower zone, died four years later from cor pulmonale, after repeated attacks of secondary infection with segmental collapse in her upper lobes. Both lungs at necropsy showed diffuse emphysema and fibrosis (Plate 47, Fig. 13), with bronchiectasis in the upper lobes. Nitter (1953) mentioned that fibrosis from sarcoidosis might be overlooked, and indirect evidence of it was found by Marshall, Smellie, Baylis, Hoyle, and Bates (1958) in five out of six of our patients who had an impaired diffusing capacity after their radiographs had returned to normal. It is evident that gauging both the onset and the remission of pulmonary sarcoidosis by radiography is subject to a margin of error for which allowance cannot be made.

With the above reservation, the radiographic course may be represented diagrammatically as in Fig. 3, where the percentages are based on Tables XII and XIII. When the initial chest radiograph shows enlarged hilar nodes

with clear lung fields there is a 71 per cent. chance of spontaneous improvement, and a 61 per cent. chance of complete radiographic clearing. Complete clearing takes rather less than a year (mean 10·3 months) from discovery, with a range from two months to two and a half years. A minority (22 per cent.) develop infiltration in both lungs, usually within a year of the discovery of the enlarged hilar nodes. Thereafter their radiographic course is similar to that of patients who show infiltration initially. Of this total group of patients with pulmonary infiltration, one-half improve spontaneously in a mean time of just over a year. The significantly better outlook, when enlarged hilar nodes are found with normal lung fields, than when pulmonary infiltration is also present, is due partly to the association of enlarged hilar nodes with erythema nodosum, and partly to the mixed composition of the group found to have pulmonary infiltration, which may have been present for more than two years before discovery, and is therefore unlikely to resolve. In all, 61 of our 125 patients have achieved a normal chest radiograph, and none of them has relapsed. In the other half of the group with pulmonary infiltration the infiltration persists, remaining unchanged in about one-fifth of the patients and increasing gradually in about two-fifths. The other two-fifths show progressive infiltration, leading eventually to gross fibrosis in about five years. At least one-tenth of the patients with increasing infiltration, and two-fifths of those with fibrosis, die from their disease. When pulmonary infiltration persists for more than two years without improving, spontaneous remission is unlikely; after three years it is rare.

To a considerable extent these observations of the natural history make it possible now to predict which patients will recover spontaneously and which will not. But they apply mainly after the disorder is at least two years old, and when it has been observed during its early course. A good prognosis can be given within this time if hilar node enlargement only is found initially, and if pulmonary infiltration does not appear within the next year (Tables XIV and XV). The chief difficulties are to forecast within two years the probable fate of pulmonary infiltration found initially, or developing after hilar node enlargement; and to recognize, at two to five years from discovery, those patients with persistent pulmonary infiltration who are likely to become respiratory cripples in the long run. There are, however, a few guides, of which the most important relates to the mode of onset: the high rate of improvement when sarcoidosis is proclaimed by an attack of erythema nodosum (Löfgren, 1953). Our patients have shown a trend towards a greater likelihood of recovery among those with no symptoms at the onset; but there is no inconsistency here, because only two of our 54 untreated patients with pulmonary infiltration have had erythema nodosum. We have found a trend also towards a better chance of spontaneous improvement when there are few extrapulmonary sites of involvement (Table V), and when the infiltration is finely nodular. Age at onset, sex, and tuberculin sensitivity have no bearing on prognosis.

Though the natural history of pulmonary sarcoidosis seems to vary widely, it has conformed with one of three chief patterns in most of our patients. One is entirely benign, with hilar node enlargement for about a year, which may or may

not be followed by pulmonary infiltration for about the same time, so that a normal radiograph may be expected at the latest in two years. A second form is more protracted. Pulmonary infiltration is always present, and often persists, but fails to advance progressively, so that eventual fibrosis is not severely destructive. Disability is slight, and the prognosis good despite enduring radiographic changes. The third type is progressive sarcoidosis, in which the lungs are infiltrated by follicles for many years. Severe fibrosis with massive disorganization of the lung is seen only in this variety, which accounts for all the major disability of the disease and its fatalities. Such striking differences in the natural history of the disorder perhaps depend upon the time for which the sarcoid process remains active in the individual host.

We wish to thank the many colleagues who referred patients, or who helped in other ways; in particular Dr. John Dawson and Dr. Gordon Mather, for some of the earlier clinical records; Mr. R. Crick for the ophthalmic investigations; Dr. L. G. Blair for advice on the radiographic classification; Professor H. A. Magnus and Dr. Brian Cardell for the pathology, and Mr. M. P. Curwen for his invaluable contributions to the statistical analyses. Mr. W. Smith and Mr. G. Harwood kindly prepared the photographs. We are indebted also to the Research Committee of King's College Hospital for a grant for expenses. The present paper is based on a thesis by one of us (H. S.) which has been accepted by the University of London for the degree of M.D.

Summary

Pulmonary sarcoidosis was found, in the present series, in 213 of 230 patients (93 per cent.). It is the commonest form of the disorder, and the usual cause of eventual disablement and death. Its clinical and radiographic features, natural course, and prognosis, have been surveyed in 125 patients followed for more than two years. It was discovered mainly by routine radiography or by investigation for uveitis or erythema nodosum, as significant respiratory symptoms occur only with progressive disease. Early pulmonary lesions were most often seen as nodular shadows (76 in 94), fine or coarse. They were diffuse (43 in 94) or concentrated mainly in the mid-zones (39 in 94), and they retained their initial pattern and distribution until remission or distortion by fibrosis occurred. Spontaneous radiographic improvement, in a mean time of one year, was achieved by 71 per cent. of patients with enlarged hilar nodes, and by 50 per cent. of those with pulmonary infiltration. A significantly better outlook was found for patients first discovered with erythema nodosum, or with hilar lymph-node enlargement and normal lung fields. None of the patients achieving a normal radiograph (61 in 125) has relapsed.

Pulmonary infiltration persisting for more than two years is unlikely to remit spontaneously. Of this group of patients two-fifths showed evidence of pulmonary fibrosis in a mean time of five years, with dyspnoea as their main symptom from then onwards. Two-fifths of these patients became respiratory cripples,

deteriorating steadily to the accompaniment of increasingly massive fibrosis, secondary infection, bronchiectasis, and bullae, with occasional haemoptysis or spontaneous pneumothorax. Cor pulmonale, which appeared in one to two decades from the discovery of their sarcoidosis, was the commonest terminal event, fatal usually within a year of the onset of heart failure.

Three main varieties of pulmonary sarcoidosis may be recognized by their natural history. Their distinctive features and prognosis are discussed.

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FIG. 4. Giant section of lung showing upper-lobe bronchiectasis and peri-bronchial fibrosis. Taken from a female patient, aged 47, who died from respiratory failure 10 years after an attack of iritis when she was found to have enlarged hilar lymph-nodes with normal lung fields. Progressive pulmonary infiltration appeared later, followed by gross fibrosis

FIG. 5. Bronchogram of the same patient 1 year before death. Both upper lobes show gross bronchiectasis

FIG. 8. Contact print of part of the right lung field, showing diffuse fine stippling in sarcoidosis

FIG. 7. Contact print of part of the right lung field, showing diffuse coarse nodular shadows in sarcoidosis

FIG. 6. Contact print of part of the right lung field, showing diffuse fine nodular shadows in sarcoidosis

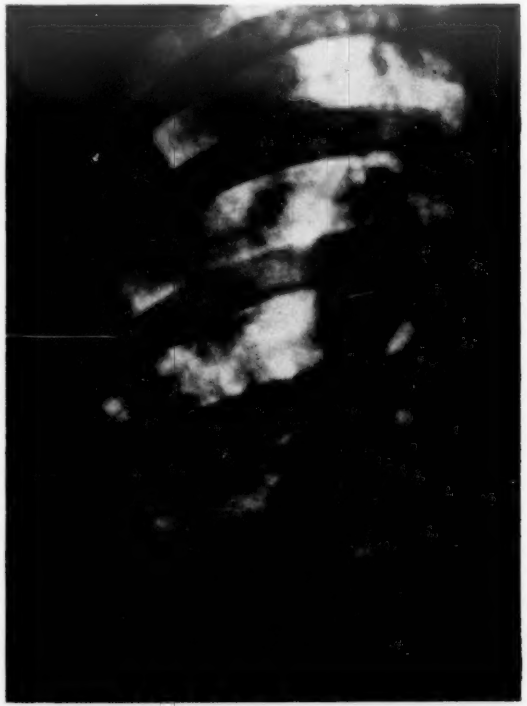

FIG. 9. Contact print of part of the right lung field, showing diffuse, patchy infiltration in sarcoidosis

FIG. 10. Contact print of part of the right lung field, showing a patchy shadow in the upper zone resembling a Ghon focus, in a patient with sarcoidosis

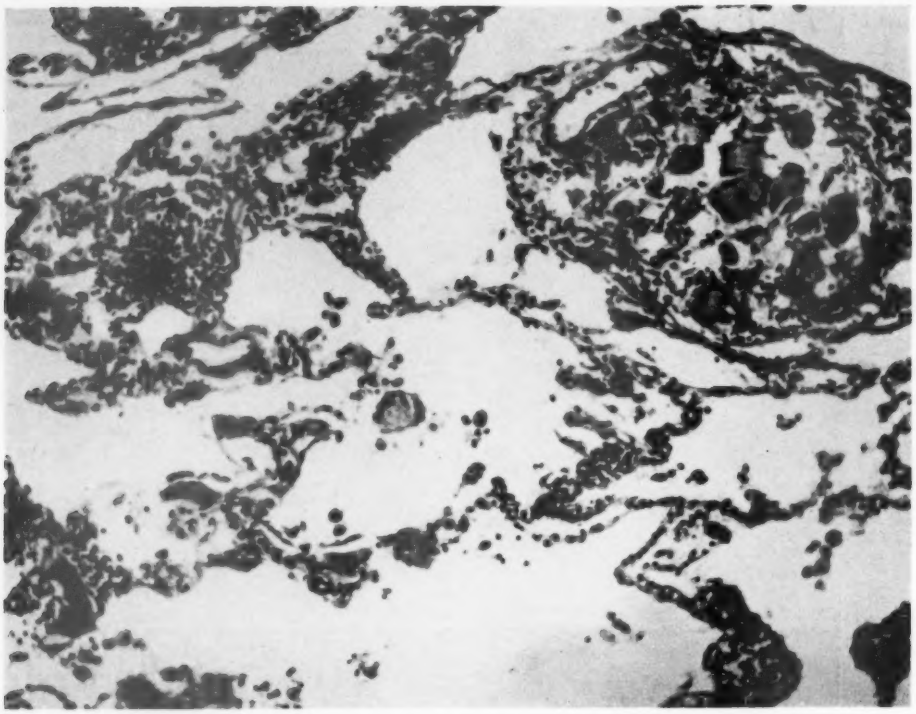

FIG. 11. Lung biopsy from a patient, aged 59, who had enlarged cervical lymph-nodes due to sarcoidosis first discovered in 1953. Her chest radiograph has always been normal. The lung biopsy was performed in 1958 because of progressive dyspnoea. The section shows an epithelioid cell follicle and fibrosis, with cellular exudate in the alveolar walls (Haematoxylin and eosin × 160)

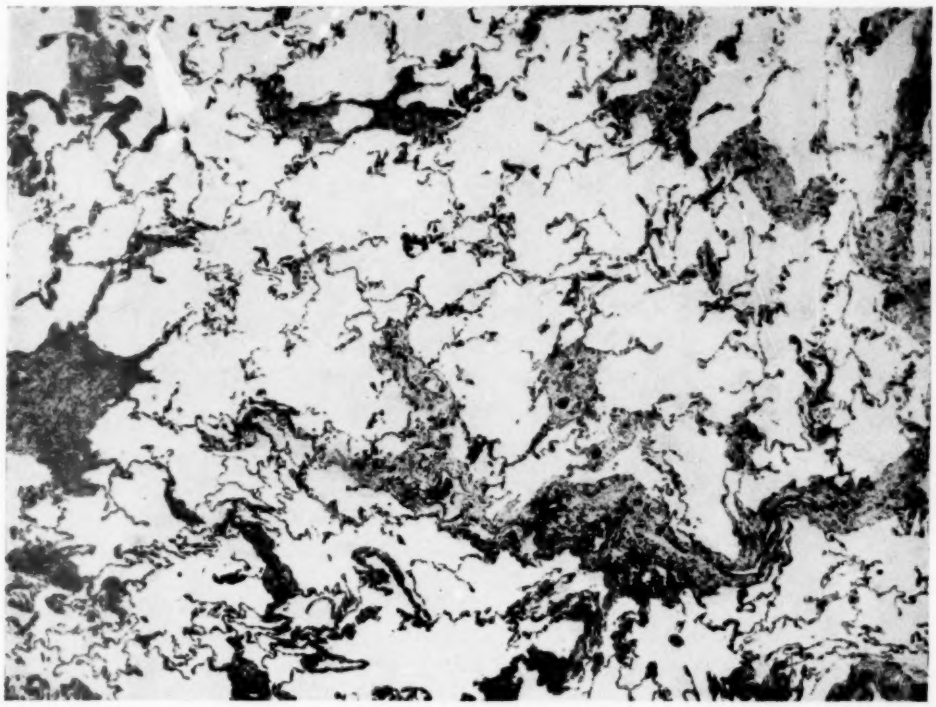

FIG. 12. Lung biopsy from a female patient, aged 44, 11 months after the discovery of bilateral enlargement of hilar nodes with diffuse nodular infiltration, due to sarcoidosis confirmed by liver biopsy, and 1 month after her radiograph had returned to normal. Microscopic areas of fibrosis are scattered throughout the lung (Haematoxylin and eosin, × 40)

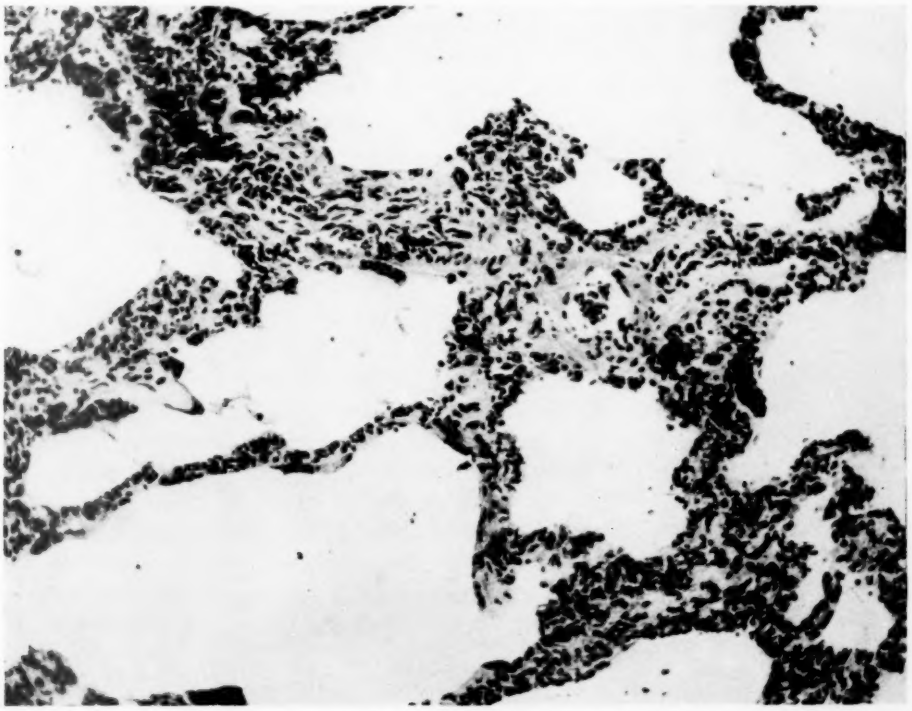

FIG. 13. Section of lung taken at necropsy from a female patient, aged 46, whose sarcoidosis started 22 years earlier with uveoparotitis. Both lungs were the seat of gross fibrosis and bronchiectasis. This section was cut from an area of lung remote from naked-eye fibrosis, and illustrates the widespread nature of fibrosis in sarcoidosis (Haematoxylin and eosin, × 160)

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A STUDY OF COR PULMONALE IN PATIENTS WITH CHRONIC BRONCHITIS[1]

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Several authors have reported the clinical findings and physiological derangements in patients with congestive cardiac failure secondary to chronic chest disease (cor pulmonale) (Baldwin, Cournand, and Richards, 1949; Harvey, Ferrer, Richards, and Cournand, 1951; Stuart-Harris and Hanley, 1957). Most of these studies, however, have been made on patients seen for the first time after heart failure had developed, probably because it is rare for any group of observers to witness the onset of failure. In Sheffield a clinic for patients with chronic chest disease has provided the opportunity for studying the physiological alterations before and after the onset of cardiac failure in the same patients. In the past eight years the patients referred from family doctors, or remaining under supervision, after treatment of an acute exacerbation of bronchitis have totalled 482. Only 23 of these patients have been seen both before and after the onset of heart failure, and in them tests of pulmonary and renal function, estimations of arterial blood gases, haemoglobin concentration, and haematocrit levels, chest radiographs, and electrocardiographs have been obtained in the different clinical phases. In 71 other patients with chest disease, who have not developed congestive failure, measurements of the pulmonary function and of the arterial blood gases served as a basis for comparison. The purpose of the present paper is to analyse the findings in order to determine which, if any, of the various measurements are helpful as a prognostic indication of the development of cardiac failure.

Methods

The nomenclature employed is that advocated in *Federation Proceedings* (1950) and by Gandevia and Hugh-Jones (1957). The diagnosis of heart failure was based on the presence of a raised jugular venous pressure in all phases of respiration, peripheral pitting oedema, and often hepatomegaly. Ventilatory function was estimated by means of the following tests: (1) *Vital capacity* was estimated by direct spirometry, and expressed as a percentage of the normal value by the formula of Baldwin, Cournand, and Richards (1948). (2) *Indirect maximum breathing capacity* (M.B.C.) was calculated by multiplying by 40 the forced expiratory volume (Kennedy, 1953). This is the volume of air expelled

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in the first 0·75 second of a forced expiration, as measured with a modified form of the spirometer described by Gaensler (1951). The maximum breathing capacity was expressed as a percentage of the expected normal value, by the formula of Baldwin, Cournand, and Richards (1948). (3) *Total lung volume and residual volume* were determined by the closed-circuit method, using helium and the apparatus described by Briscoe (1952). The volume of the functional residual capacity was calculated from the measured final concentration of the helium. The patient's expiratory reserve volume was deducted from the functional residual capacity to obtain the residual volume, and this was expressed as a percentage of the total lung volume. (4) *The impairment of the efficiency with which inspired helium was mixed in the lungs* was graded arbitrarily by inspection of graphs, in which the concentration of helium in the spirometer was plotted semilogarithmically against the number of respirations. Four grades were recognized, ranging from 0 (normal mixing) to 3 (very severely impaired mixing) (Stuart-Harris and Hanley, 1957). The efficiency of mixing was assessed independently by Dr. Marjorie Clifton, who was unaware of the patients' clinical condition.

Oxygen saturation and carbon-dioxide tension of the arterial blood. All measurements of arterial blood gases were made when the patients were at rest. Arterial blood was obtained from the brachial artery with a syringe which had been rinsed out with a heparin solution. The pH of the blood was immediately measured with a battery-operated pH meter and a glass electrode in a Stadie-type electrode holder surrounded by water at room temperature. The apparatus was standardized before each estimation with a buffer solution of pH 7·40. The pH was corrected to 38° C by subtracting (0·014 × [38° minus temperature of the water bath]) pH units from the observed value (Rosenthal, 1948). Duplicate readings agreeing to 0·01 were regularly obtained. The total concentration of CO_2 and the oxygen content and capacity of the blood were measured by the manometric method of Van Slyke and Neill (1924). The partial pressure of CO_2 was derived from the nomogram of Singer and Hastings (1948), by using the measured values of whole blood CO_2 content, pH, and haematocrit. Haemoglobin concentration of blood was measured either by dividing by 1·34 the oxygen capacity as determined with the Van Slyke apparatus, or colorimetrically by using a spectrophotometer (Evans Electroselenium Ltd.).

Cardio-thoracic ratio. All the X-rays of the chest were standard six-foot postero-anterior films. The cardio-thoracic ratio was obtained by dividing the greatest transverse diameter of the heart by the width of the thoracic cage at the same level.

Electrocardiograms were recorded with the 12 standard leads.

Renal clearances. Renal plasma flow was measured with para-aminohippuric acid (PAH) and the glomerular filtration rate with inulin. PAH and inulin were given intravenously together with an intramuscular injection of PAH (Dick and Davies, 1949). Two or three 20-minute clearance periods were measured in each case, and the results expressed as absolute values uncorrected for the patient's body-surface area.

TABLE I

Clinical Histories of Patients who Developed Heart Failure while under Observation

Patient	*Sex*	*Age when first seen (years)*	*Occupation*	*Pulmonary disease*	*Length of follow-up (months) before onset of heart failure*	*Past history of respiratory illnesses*	*Duration of cough when first seen*	*Duration of breathlessness when first seen*	*Blood-pressure (mm. Hg) when first seen*
1	M	57	Coal miner	Bronchitis, emphysema, pneumoconiosis—grade 3	6	None	4 years	4 years	120/75
2	M	60	Joiner	Bronchitis, emphysema	13	Gassed in 1914–18 war	40 years	2 years	170/110
3	F	31	Housewife	Pulmonary eosinophilia, asthma, emphysema	30	None	6 years	6 years	125/80
4	M	62	Ingot maker	Bronchitis, emphysema	24	Pneumonia aged 52 years	10 years	10 years	135/75
5	M	40	Warehouseman	Bronchitis, emphysema	15	Pneumonia in childhood	Since childhood	1 month	190/105
6	M	53	Labourer	Fibrosis, bronchiectasis	5	None	7 years	1 year	120/40
7	M	50	Power press operator	Bronchitis, emphysema	35	Pneumonia in infancy	1 year	1 year	135/85
8	M	51	Coal miner	Bronchitis, emphysema	16	None	20 years	15 years	135/95
9	M	46	Labourer—steel	Bronchitis, emphysema	11	Pneumonia in childhood	Since childhood	10 years	140/90
10	M	48	Grinder, boiler-firer	Bronchitis, emphysema	15	Pneumonia aged 42 years	6 years	6 years	150/100
11	M	27	Worker in rolling-mill	L. lower lobe collapse, bronchiectasis	52	7 attacks pneumonia, first when aged 10 years	Since childhood	None (developed 3 years later)	140/85
12	M	41	Coal miner	Bronchitis, emphysema, bronchiectasis	80	Pneumonia aged 34 years	7 years	7 years	115/80
13	M	41	Spring-maker	Bronchitis, emphysema	68	None	10 years	10 years	115/65
14	M	58	Farmer	Bronchitis, emphysema	39	Pneumonia aged 51 years	20 years	6 years	130/70
15	M	46	Grinder, steel worker	Bronchitis, emphysema	7	None	5 years	5 years	130/90
16	M	30	Shop manager	Bilateral bronchiectasis	76	Pneumonia aged 8 years	22 years	Several years	110/60
17	M	48	Worker in rolling-mill	Bronchitis, emphysema	6	Empyema and pneumonia aged 45 years	3 years	5 months	120/80
18	M	62	Clerk	Bronchitis, emphysema	38	Pneumonia aged 61 years	8 years	1 year	140/70
19	M	52	Cobbler	Bronchitis, emphysema	87	Pneumonia aged 49 years	12 years	3 years	140/70
20	M	55	Civil servant	Bronchitis, emphysema	100	Gassed in 1914–18 war	2 years	Few months	180/105
21	M	55	Coal miner	Bronchitis, emphysema silicosis	33	None	20 years	2 years	140/70
22	M	53	Forge-hand	Bronchitis, emphysema	20	None	10 years	2 years	130/80
23	M	48	Cutler	Bronchitis, emphysema	5	None	10 years	6 weeks	140/80

Results

Patients studied. The general findings in the patients attending the chest clinic have already been described in detail (Stuart-Harris and Hanley, 1957). Most suffer from chronic bronchitis of varying grades of severity, but some have bronchiectasis, asthma, or pneumoconiosis. Of the 23 patients who developed cardiac failure while under observation, three had severe bronchiectasis, one asthma and emphysema, and the remainder chronic bronchitis and emphysema (Table I). Only one patient was female. Nineteen have died, and the clinical diagnosis of cor pulmonale was confirmed in seven patients on whom autopsies were performed. For convenience of description these 23 patients are hereafter referred to as 'cardiac' patients.

TABLE II

Results of the First Respiratory Function Tests Performed on the Patients who Developed Heart Failure while under Observation

	First respiratory function tests				*First arterial blood measurement*		
Patient	*Vital capacity (% of predicted)*	*Residual volume / Lung volume (%)*	*M.B.C. (% of predicted)*	*Time before first heart failure (months)*	*$_pCO_2$ (mm. Hg)*	*Oxygen saturation (%)*	*Time before first heart failure (months)*
1	53	76	21	6	65	71	6
2	54	73	..	13	47	89	13
7	55	..	24	11	51	90	35
8	74	68	38	16	52	85	17
9	85	63	36	11	52	79	11
10	64	62	25	15	55	79	15
12	64	75	31	32	57	85	41
13	62	61	39	34	56	80	20
14	70	60	38	19	54	81	11
15	77	62	21	7	66	76	6
17	50	67	26	6	54	76	7
19	68	72	36	49	53	83	40
20	42	72	18	13	49	87	14
21	67	70	48	31	52	75	11
23	49	70	21	16	60	68	5
3	..	..	..	..	..	81	1
4	..	..	..	..	..	82	15
5	..	..	..	..	..	82	17
6	..	..	..	..	49	85	5
11	..	..	..	..	47	73	½

M.B.C. = indirect maximum breathing capacity.

Ventilatory Function and Arterial Blood Gases

1. *Before cardiac failure.* Table II shows the results of the first measurements of ventilatory function and arterial blood gases in 20 of the 23 'cardiac' patients. The tests had been made at periods of from six to 49 months before they developed heart failure. The pattern of ventilatory disturbance was typical of the findings in chronic bronchitis and emphysema; there was a reduction in the vital capacity and indirect maximum breathing capacity, and a high residual lung volume. The degree of abnormality is best seen by comparing the results

with those in the 71 patients who have not yet developed cardiac failure (Fig. 1). There is a wide scatter of the measurements of vital capacity in both 'cardiac' and other patients. Residual lung volumes in excess of 63 per cent. of the total lung capacity were more common among the 'cardiac' patients. The maximum

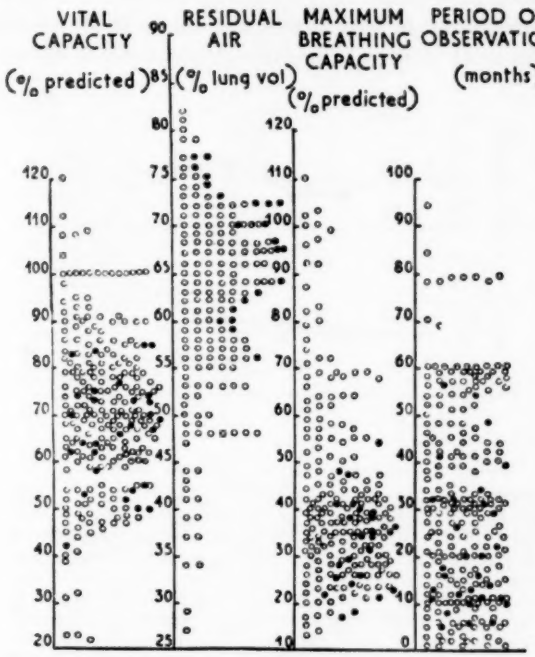

FIG. 1. Measurements in 23 'cardiac' patients (black circles) and 71 patients with chronic bronchitis and emphysema who have never developed heart failure (open circles). The vital capacity was below 75 per cent. of the predicted value in 75 per cent. of the 'cardiac' patients and in 56 per cent. of the bronchitics; the residual air constituted more than 64 per cent. of the lung volume in 75 per cent. of the 'cardiac' patients and in 55 per cent. of the bronchitics; the maximum breathing capacity was below 40 per cent. of the predicted value in 75 per cent. of the 'cardiac' patients and in 53 per cent. of the bronchitics. Ninety-five per cent. of the 'cardiac' patients and 81 per cent. of those with chronic bronchitis were observed for longer than 10 months.

breathing capacity was below 40 per cent. of the predicted normal values in 75 per cent. of the 'cardiac' patients, and in 53 per cent. of those who had not developed heart failure. Of the 71 patients with chronic bronchitis whose ventilatory function is shown in Fig. 1, approximately two-thirds exhibited the arbitrarily defined second grade, and one-third showed the severest third grade, of mixing defect. Equal proportions of 'cardiac' patients showed a second and third grade of mixing defect. Serial measurements of the ventilatory function in five 'cardiac' patients, who were studied repeatedly before the onset of heart

failure, are shown in Fig. 2. One patient showed a steady deterioration in vital capacity, maximum breathing capacity, and residual lung volume, but the other four all exhibited a relatively unchanging restriction of ventilatory function.

The arterial blood gases of all the patients studied on one or more occasions are shown diagramatically in Fig. 3, and the values in 20 'cardiac' patients studied two weeks to 41 months before the development of cardiac failure are

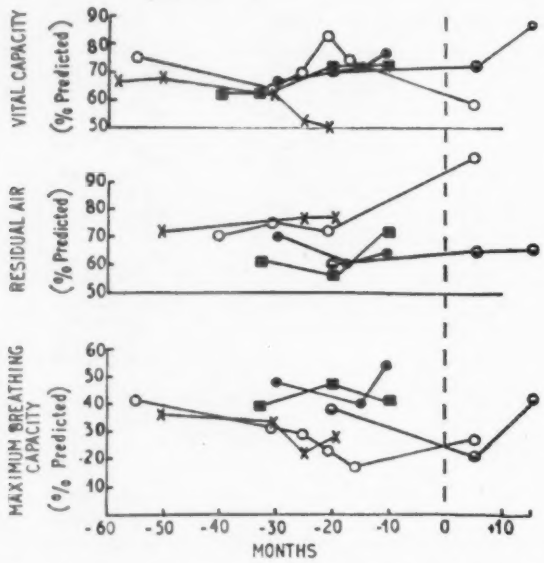

FIG. 2. Pulmonary function studies in five patients at various intervals of time before the development of heart failure. The interrupted line (0) shows the time of onset of heart failure.

shown in Table II. In contrast to the ventilatory tests, the carbon-dioxide tension and arterial oxygen saturation were more often severely abnormal in the 'cardiac' than in the other patients. Thus the first measurements of the carbon-dioxide tension ranged from 47 to 66 mm. Hg, and 75 per cent. of all the measurements in the 'cardiac' patients were over 49 mm. Hg. Only 24 per cent. of the other patients had similarly high values. When the patients were first seen the oxygen saturation of the arterial blood was between 68 and 90 per cent., while three-quarters of all the values were under 86 per cent. in the 'cardiac' patients. Only one-third of the other patients had a similar reduction in oxygen saturation. The arterial gases were abnormal for long periods before the onset of heart failure. Thus, in the three patients studied most frequently, the carbon-dioxide tension was in excess of 50 mm. Hg for between one and four years before heart failure occurred (Fig. 4). A deterioration occurred during the following months, and the oxygen saturation tended

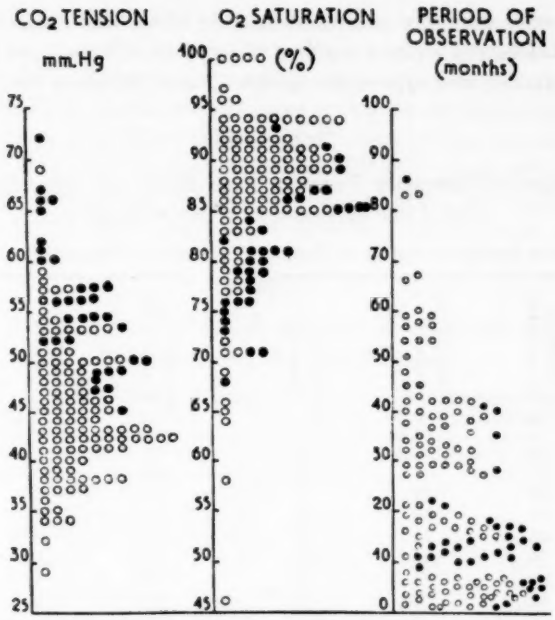

FIG. 3. The arterial blood gases of all patients studied on one or more occasions. Black circles = 'cardiac' patients; open circles = patients with chronic bronchitis who have never developed heart failure. The carbon-dioxide tension was more than 49 mm. Hg. in 75 per cent. of the 'cardiac' patients and in 24 per cent. of the bronchitics; the oxygen saturation was below 86 per cent. in 75 per cent. of the 'cardiac' patients and in 30 per cent. of the bronchitics. Seventy-five per cent. of the 'cardiac' patients and 68 per cent. of those with chronic bronchitis were observed for longer than nine months.

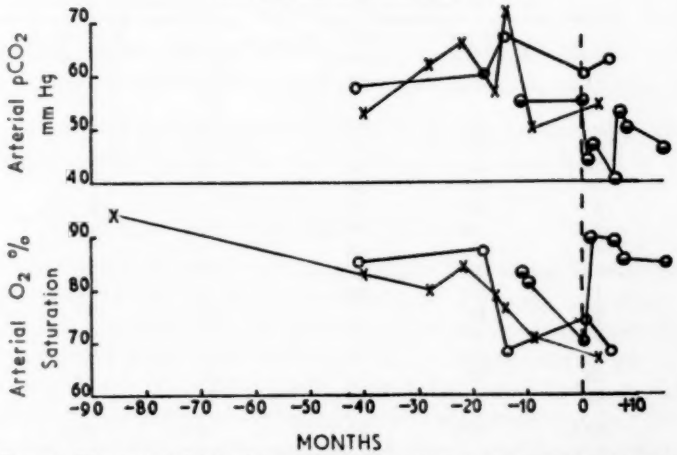

FIG. 4. The arterial blood gases in three patients before and after the development of heart failure. The interrupted line (0) shows the time of onset of heart failure.

to fall. The only normally saturated arterial blood was obtained as long as seven years before the patient yielding the specimen developed heart failure.

2. *Before, during, and after heart failure.* Table III gives the results of the

TABLE III

Changes in Pulmonary Function Tests Before and After Recovery from First Development of Heart Failure

	Before development of heart failure			*After development of heart failure*		
Patient	*Vital capacity (% of predicted)*	*Residual volume / Lung volume (%)*	*M.B.C. (% of predicted)*	*Vital capacity (% of predicted)*	*Residual volume / Lung volume (%)*	*M.B.C. (% of predicted)*
2	54	73	34	70	71	51
7	58	..	24	66	69	..
8	83	59	34	69	65	39
9	85	63	36	70	65	37
10	64	62	25	75	57	32
14	70	60	38	72	65	26
17	50	67	26	49	63	25
19	42	72	18	31	75	16
Mean	63·3	65·1	29·4	62·8	66·3	32·3

The last readings made before the first onset of heart failure are compared with the first readings made after recovery from the first attack of heart failure.

M.B.C. = indirect maximum breathing capacity.

TABLE IV

Arterial Blood Gases Before, During, and After Recovery from Heart Failure

	pCO_2 (mm. Hg)			*Oxygen saturation (%)*		
Patient	*Before*	*During heart failure*	*After recovery*	*Before*	*During heart failure*	*After recovery*
2	45	47	44	91	88	96
4	..	..	..	82	77	..
5	..	63	64	82	62	73
6	49	69	..	85	77	..
7	54	64	64	90	63	63
9	56	53	53	79	57	80
10	57	64	56	78	65	73
11	60	65	60	73	41	75
12	63	..	63	76	..	68
13	56	59	..	74	74	..
14	49	55	44	76	70	90
15	66	66	..	76	70	..
17	54	59	84	76	70	69
19	50	54	..	71	67	..
20	49	63	..	87	75	..
23	60	..	65	68	..	69
Mean	54·9	60·1	59·7	79·0	68·3	75·6

The values used in this table are the last obtained before and the first available during and after recovery from heart failure.

ventilatory tests in eight patients studied before, and again some time after, the development of cardiac failure and its treatment with antibiotics, diuretics, and antispasmodics. There was remarkably little fluctuation in the ventilatory function. Table IV shows the arterial gases in 16 patients studied before, during, and after recovery from heart failure. The values obtained during and after failure showed the alterations already reported (Platts, 1953), with high carbon-dioxide tension in all clinical phases and a change from a state of severe oxygen unsaturation during failure to one of moderate unsaturation after loss of

TABLE V

Changes in Haemoglobin and Mean Corpuscular Haemoglobin Concentration in Patients Developing Heart Failure

	Haemoglobin (g./100 ml.)					*Mean corpuscular haemoglobin concentration (%)*		
	Before onset of failure				*In failure*	*Before onset of failure*		*In failure*
Patient	*First*	*(months before failure)*	*Last*	*(months before failure)*		*First*	*Last*	
1	17·5	(5)	15·4	(1)	15·2	32·9	29·6	29·2
2	..	..	13·5	(13)	15·7	..	31·4	36·5
3	14·5	(27)	14·3	(4)	14·9	30·6	30·2	31·7
4	14·0	(24)	14·9	(12)	12·5	33·4	32·4	30·5
5	..	..	18·2	(15)	17·1	..	30·4	30·5
7	14·6	(32)	13·6	(3)	17·3	31·7	27·2	31·5
8	18·6	(14)	16·4	(11)	16·9	33·2	30·4	32·5
12	15·1	(74)	15·6	(18)	17·5	30·2	28·3	27·4
13	13·8	(44)	14·8	(20)	14·1	30·7	29·0	30·0
14	15·7	(28)	16·1	(10)	16·3	29·1	31·6	29·6
16	16·1	(78)	11·8	(38)	13·6	33·5	29·5	30·3
17	..	..	16·6	(6)	16·3	..	30·2	28·6
19	17·1	(77)	14·6	(10)	14·1	32·3	27·6	23·1
20	15·9	(46)	16·3	(14)	15·2	32·5	33·3	29·3
21	16·7	(20)	16·7	(12)	15·0	32·1	31·5	29·4
23	..	..	15·3	(20)	13·3	..	31·2	26·1
Mean	15·8	(39·1)	15·3	(12·9)	15·3	31·9	30·2	29·8

N.B. None of these patients had had a venesection when these measurements were made.

oedema. The carbon-dioxide tension and the oxygen saturation were, however, slightly less abnormal before than after recovery from heart failure.

Other Measurements made Before and After Heart Failure

1. *The haemoglobin, haematocrit level, and mean corpuscular haemoglobin concentration.* Most of the 'cardiac' patients had a higher concentration of haemoglobin than normal (14·8 g. per cent.) in their blood, the average of 46 readings performed before they developed failure being 15·2 g. per 100 ml. The average of 150 readings from the 71 other patients was 15·4 g. per 100 ml., and therefore the haemoglobin concentration was not found to be of differential value. The haemoglobin concentration did not change significantly either before or after heart failure had developed (Table V).

The mean of all the values of mean corpuscular haemoglobin concentration in the patients who have not developed heart failure was 32·0 per cent., compared with 31·0 per cent. in the 'cardiac' patients, in whom this value tended to fall as the disease progressed. Only one of the 'cardiac' patients had a mean corpuscular haemoglobin concentration below 30 per cent. when first seen, and the average value for the group, five to 78 months before the onset of heart failure, was 31·9 per cent. The last estimate made before the onset of heart failure was lower than the first in 10 out of 12 patients. A further reduction occurred in nine out of 16 patients after they had developed heart failure, by which time half of these patients had a mean corpuscular haemoglobin concentration below 30 per cent. This change was the result of a tendency of the haemoglobin concentration to fall, and the haematocrit level to rise slightly, during the period of observation. The average of all the haematocrit values in the patients without heart failure was 48·2 per cent., and in the 'cardiac' patients 49·1 per cent.

TABLE VI

Changes in the Cardio-thoracic Ratio in Patients Developing Pulmonary Heart Failure

Patient	*Cardio-thoracic ratio approximately 1 year before onset of cardiac failure*	*After onset of cardiac failure*	
		Cardio-thoracic ratio (first film)	*Clinical state*
2	44·5	43·4	Recovering
7	37·5	43·2	N.F.
9	36·2	41·8	F.
10	44·2	49·1	F.
13	43·6	50·8	F.
14	43·8	48·9	F.
16	44·3	59·3	F.
17	45·4	55·9	F.
19	44·0	59·4	F.
20	49·1	64·8	F.
21	40·0	39·3	N.F.
23	42·4	44·1	Recovering
Mean	42·9	50·0	

F. = In failure.
N.F. = Recovered from failure.

2. *The cardio-thoracic ratio* of all the 'cardiac' patients was normal one year before the onset of heart failure. When the patients became oedematous the index invariably increased, but tended to fall again when recovery took place (Table VI). The increase in heart size occurred simultaneously with the development of heart failure, and did not precede it.

3. *Electrocardiograms.* Of the 23 'cardiac' patients, 17 had a complete 12-lead electrocardiogram recorded both before and during the first attack of heart failure. In four patients the records taken before the onset of cardiac failure were normal, and in 13 patients various abnormalities were present (Table VII). The commonest abnormality was a late R wave in aVR, which was found in 12 of the 17 patients. A 'P pulmonale' was present in six patients, and the

QRS complex in V1 was abnormal in seven. Four patients showed inversion of the T waves in the right ventricular precordial leads. With the development of heart failure an increase occurred in the frequency of a late R wave in aVR, of T-wave inversion in leads V1 to V3, and of delayed intrinsic deflection or an RSR' pattern in V1. In two patients a 'P pulmonale' disappeared with the onset of heart failure, and in one it first appeared at this time. In one patient the electrocardiogram was normal both before and after the onset of heart failure. Included in Table VII for comparison are the electrocardiographic findings in 85 patients with chronic bronchitis described by Stuart-Harris and

TABLE VII

The Electrocardiogram in 17 Patients in whom it was Recorded Before and During Heart Failure

	Before failure	*During first attack of failure*	*85 patients with bronchitis alone*
Normal pattern . .	4 (24)	1 (6)	63 (74)
'P pulmonale' . .	6 (35)	5 (29)	5 (6)
Late R wave in aVR (qR pattern) . . .	12 (70)	14 (82)	14 (16)
Delayed intrinsic deflection in V1 etc.* . .	3 (18)	4 (24)	0
Incomplete right bundle branch block (RSR') pattern in V1 . .	4 (24)	7 (41)	4 (5)
Inversion of T wave in V1–3	4 (24)	9 (53)	4 (5)

Figures in brackets are percentages.

*Reversal of R/S ratio in leads V1 and V6, tendency to small Q in V1, inverted T in V1 and upright T in V6, QRS less than 0·12 second and absence of notching of R wave in V1 (Myers, Klein, and Stofer, 1948).

Hanley (1957). The abnormalities recorded in these patients, who have never developed cardiac failure, are similar to those found before and after the onset of heart failure in the present series of patients with cor pulmonale. Two differences exist, however: the incidence of the abnormalities was much lower in patients who have never developed heart failure, and none of these patients showed a delayed intrinsic deflection in V1, which Myers, Klein, and Stofer (1948) considered to be essential for a definite diagnosis of right ventricular hypertrophy.

Eight of the 17 patients in whom electrocardiograms were recorded before the onset of heart failure had abnormal QRS complexes in V1 or abnormal P waves. Table VIII shows the length of time which elapsed between the first electrocardiographic recordings, the development of these abnormalities, and the onset of heart failure, in each of the eight patients. In four patients one or more of the abnormalities were present in the first record, from six to 20 months before heart failure appeared. Of the abnormalities which developed in serial records taken before the onset of cardiac failure, a 'P pulmonale' was noted in three patients, delayed intrinsic deflection of V1 in two, and RSR' pattern in V1 in one patient. In all three patients who developed a 'P

pulmonale' this abnormality appeared less than nine months before the onset of heart failure.

4. *Renal clearances* were measured in 15 of the 23 patients who developed heart failure. Unfortunately, observations before and after the onset of failure in the same patients were made in only four cases (Table IX). Clearances were estimated on 13 occasions in 11 patients from five to 61 months before the onset of heart failure. The glomerular filtration rate was over 100 ml. per

TABLE VIII

The Development of Abnormalities in Serial Electrocardiograms taken in Eight Patients Before the Onset of Heart Failure

	Time in months before onset of heart failure			
Patient	*First record*	*'P pulmonale'*	*Delayed intrinsic deflection in V1*	*RSR' pattern in V1*
7	35	3	..	..
9	12	..	12	..
12	86	3	21	..
13	66	7	7	..
15	10	10	..	..
17	6	6	..	6
19	77	..	..	13
22	20	20	..	20

TABLE IX

Glomerular Filtration Rate and Renal Plasma Flow in Patients Developing Heart Failure

	Before first attack of heart failure				*During first attack of heart failure*			*After recovery from heart failure*		
Patient	*Months before failure*	*Glomerular filtration rate (ml./min.)*	*Renal plasma flow (ml./min.)*	*Filtration fraction*	*Glomerular filtration rate (ml./min.)*	*Renal plasma flow (ml./min.)*	*Filtration fraction*	*Glomerular filtration rate (ml./min.)*	*Renal plasma flow (ml./min.)*	*Filtration fraction*
1	6	65	236	0·28						
	5	129	409	0·32						
2	13	130	660	0·20						
3	21	101	535	0·19						
4	15	80	240	0·33						
5	15	112	336	0·33	86	187	0·46			
6	..	..	..	..	85	228	0·37			
7	..	..	..	..	94	240	0·39	63	207	0·30
9	11	67	248	0·27	61	132	0·46	97	354	0·27
10	..	..	..	..	162	314	0·52	157	453	0·35
11	..	..	..	..	127	337	0·38			
12	61	56	237	0·24						
	21	112	327	0·34						
13	20	90	384	0·23						
15	6	119	299	0·40						
19	12	70	250	0·28	59	170	0·35			
23	5	96	489	0·20	..	..	..	43	168	0·26
Mean	16·2	94·3	357·7	0·278	96·3	229·7	0·419	90·0	295·5	0·295
Normal values (Smith, 1951)		124 ±26	600 ±124	0·192 ±0·035						

minute on six occasions, and was moderately reduced on the other seven. The renal plasma flow, measured simultaneously, was reduced in 11 of the 13 measurements. As a result the filtration fraction was higher than normal in eight of the 13 estimations. In the four patients studied before and after the onset of heart failure there was a further reduction in glomerular filtration rate and renal plasma flow when congestion occurred. The reduction in plasma flow was relatively greater than that in glomerular filtration, so that there was a further increase in the filtration fraction. In seven clearances performed during heart failure there was a reduction in both the glomerular filtration and the renal plasma flow in all but two patients, in whom the glomerular filtration was within the normal range but the plasma flow reduced. A high filtration fraction was thus the commonest abnormality during failure.

Discussion

Relatively few prospective studies of patients with chronic bronchitis and emphysema have yet been made. Bates, Knott and Christie (1956) observed a series of 59 patients with emphysema and a history of chronic bronchitis, and followed them up for a period of five years. In this time 17 patients died, of whom 13 had developed pulmonary heart failure. Repeated estimation of the vital capacity, functional residual capacity, and mixing efficiency did not suggest a close correlation between the severity of ventilatory defect and the prognosis. But the diffusing capacity, as measured by the uptake of carbon monoxide, was observed to fall progressively in patients with a poor prognosis, especially when right ventricular failure was imminent. The authors considered that this reduction in diffusing capacity was due chiefly to a loss of effective surface for gas exchange, though they did not comment on the fact that airway obstruction causes a defect in carbon-monoxide uptake as readily as does a loss of blood-gas interface. Our own studies agree with the above findings in that the vital capacity, maximum breathing capacity, and residual volume bore little relation to the development of congestive heart failure. But a high carbon-dioxide tension and unsaturation with oxygen of the arterial blood were noted more frequently in the patients in whom heart failure was later to occur than in the other patients with chronic bronchitis. It has repeatedly been shown (Cournand, 1950; Fishman, Samet, and Cournand, 1955; Stuart-Harris and Hanley, 1957) that this combination of arterial oxygen unsaturation and carbon-dioxide retention implies a reduced alveolar ventilation which may, of course, be consequent upon airway obstruction. It is clear from our observations that alveolar hypoventilation precedes the development of right ventricular failure in patients with chronic bronchitis and emphysema, though its existence does not signify the immediate imminence of failure. There are also some patients with chronic chest disease in whom heart failure develops in the absence of carbon-dioxide retention: for instance, patients with thrombosis or embolism of the pulmonary circulation. In such instances a mechanism exists for the failure of the circulation different from that which is present in chronic bronchitis.

Although anoxia was more severe in the patients who subsequently developed heart failure than it was in the other bronchitic patients, the haemoglobin concentration was similar in the two groups. There was no evidence of haemodilution, which might have masked a rise in haemoglobin concentration in the patients with heart failure, since there was no reduction in the packed cell volume at this time. The findings confirm previous reports (Harvey, Ferrer, Richards, and Cournand, 1951; Hecht, 1956) that the concentration of haemoglobin in the red cells is reduced in severe emphysema.

The electrocardiograms were much more commonly abnormal in the 'cardiac' patients, before the onset of heart failure, than in other patients with chronic bronchitis who have never developed heart failure. The abnormalities in these records were similar to those described by previous workers in patients with cor pulmonale (Wood, 1947; Myers, Klein, and Stofer, 1948; Kilpatrick, 1951; Mounsey, Ritzmann, and Selverstone, 1952). Consideration of the abnormalities as they occurred in serial records, taken before the onset of heart failure, showed that the development of a 'P pulmonale' usually indicated that heart failure would develop within a few months. The electrocardiographic changes which occurred with the onset of cardiac failure were merely quantitative, as Stuart-Harris and Hanley (1957) have already pointed out. Measurements of the cardio-thoracic ratio showed that a sudden increase in heart size occurred when the patients first developed heart failure, but did not precede it. The enlargement of the cardiac shadow is presumably the result of dilatation rather than hypertrophy.

The renal plasma flow was reduced more often, and to a greater extent, than the glomerular filtration rate, and the filtration fraction was therefore increased, in the majority of patients studied before the onset of heart failure. This result differs from the findings of Stuart-Harris, Mackinnon, Hammond, and Smith (1956), who found approximately normal filtration fractions in patients with chronic lung disease which had not been complicated by the development of cardiac failure. With the onset of heart failure there was a further increase in the filtration fraction in the four patients studied before and after the development of this complication, and a very high filtration fraction characterized the findings in the other patients who were studied only after heart failure occurred. The changes associated with heart failure are similar to those reported by previous workers (Davies and Kilpatrick, 1951; Stuart-Harris, Mackinnon, Hammond, and Smith, 1956). It thus appears that the increase in the filtration fraction, which characterizes the renal circulation in patients with all forms of heart failure, was present for many months before the development of oedema. The possible importance of this change in the renal circulation in the aetiology of salt and water retention has recently been stressed by Vander, Malvin, Wilde, and Sullivan (1958).

In conclusion, the present study has confirmed the fact that there is no single reliable index of impending heart failure in patients with chronic lung disease. The length of history, the clinical findings, and the observed disturbance in ventilatory function are of little avail in the assessment of the degree of involve-

ment of the cardiovascular system. The electrocardiogram and the renal clearance may also fail to indicate the imminence of heart failure. Nevertheless, the finding of a 'P pulmonale' in the electrocardiogram, or of an increase in the filtration fraction, is probably indicative of serious involvement of the circulation in patients with chronic disease of the lung. Even more important from a prognostic standpoint are the alterations in the arterial blood gases which have been described. The existence of a raised carbon-dioxide tension, and of unsaturation of the arterial blood with oxygen, in patients examined at rest, is in our opinion the best evidence available at present of the likelihood of ultimate congestive heart failure. It is a matter for speculation whether it may be possible to prevent further deterioration in function at this stage of the disease by measures such as salt restriction.

Summary

1. Twenty-three patients with chronic chest disease have been studied before and after the development of congestive heart failure (cor pulmonale).

2. There was no greater severity of ventilatory defect, as determined by the vital capacity, indirect maximum breathing capacity, and measurement of the residual volume and mixing efficiency in these patients, than in a group of 71 other patients with chest disease but without heart failure.

3. The arterial blood exhibited a higher carbon-dioxide tension, and a lower percentage oxygen saturation, in 20 of the 'cardiac' patients before heart failure than in the other patients. Abnormal blood-gas values existed for several months, or years, before signs of heart failure were elicited, but worsened during the latter period.

4. The haemoglobin percentage remained normal, but the mean corpuscular haemoglobin concentration fell, before the onset of heart failure.

5. Electrocardiographic abnormalities were present in 13 of 17 patients examined before the onset of failure. They were present in a greater percentage of these patients than of patients with chronic bronchitis alone. A 'P pulmonale' and an abnormal QRS complex in V1 were found to precede the development of heart failure.

6. Renal function was studied in 11 patients before heart failure was present. There was a normal mean glomerular filtrate rate, a reduced renal plasma flow, and a higher than normal filtration fraction. These changes persisted during and after heart failure.

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FACTORS IN THE PROGNOSIS OF BLEEDING CHRONIC GASTRIC AND DUODENAL ULCERS[1]

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Much has been written about bleeding peptic ulcers, but the subject is by no means exhausted. Many patients, especially older ones, die from the condition, and prognostic factors require further elucidation. Two in particular have received relatively little attention. Howarth and Sharpey-Schafer (1947) showed that important changes occurred in the cardiovascular system after haemorrhage. There has, however, been little comment on the significance of this work in clinical practice, although Stewart, Cosgriff, and Gray (1956) noted a few patients who died after operation for gastroduodenal haemorrhage with 'cardiac decompensation', and a few others with 'decompensation and pulmonary oedema' who survived; and Wirts and Bodi (1957) mentioned three patients who died in congestive heart failure. There are few accounts in which the results of bleeding from chronic gastric ulcers and from duodenal ulcers are given separately. Examination of the comparative results of medical treatment and of emergency surgery in a few series revealed the possibility of important differences in prognosis in respect of patients with chronic gastric and duodenal ulcers (Chinn and Weckesser, 1951; Jones, 1956). These are not the only factors in prognosis which deserve further consideration. We report the results of treatment in patients bleeding from simple chronic gastric and duodenal ulcers who have been admitted to a general medical unit of a large area hospital. Various factors influencing the prognosis in this type of case are discussed.

The Present Series

In one of the three general medical units of this hospital, during 11 years from 1947 to 1958, there were 325 admissions, involving 300 patients, for bleeding chronic gastric and duodenal ulcers. The ulcer was demonstrated in every case by X-rays, gastroscopy, operation, or autopsy. Ulcers were classed as chronic only when they were thought to involve destruction of more than mucosa and muscularis mucosae. No patients with acute erosions, or in whom the site of haemorrhage was uncertain, have been included in the series. It was possible to perform early barium-meal examinations or gastroscopy in only a few cases, and so the site of the ulcer was often not known at the time when surgical treatment was being considered. Of the 325 admissions, chronic gastric ulcers were

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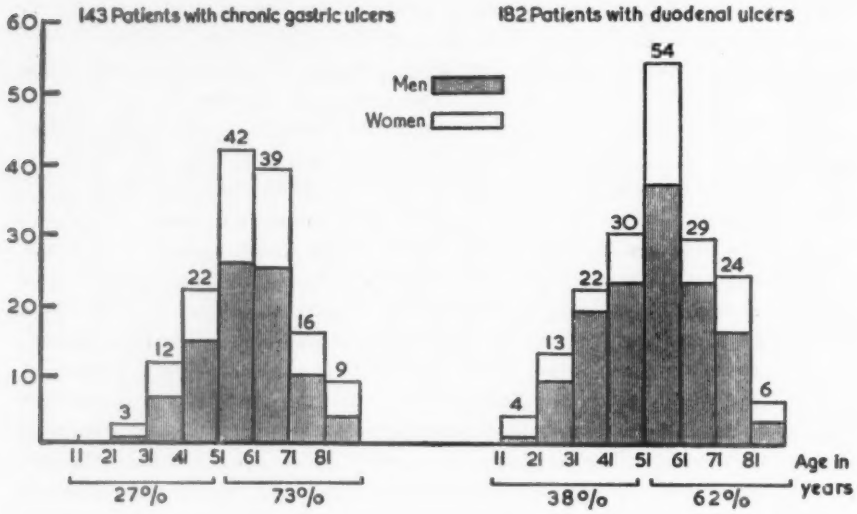
present in 143 (44 per cent.) and duodenal ulcers in 182 (56 per cent.). Patients with both gastric and duodenal ulcers have been excluded from the series.

Factors in Prognosis

In order to assess the value of various factors in prognosis, the patients were grouped according to these factors, and the mortality examined in each group.

The site of the ulcer (Table I). Twenty-nine (20 per cent.) of 143 cases of chronic gastric ulcer, and 14 (8 per cent.) of 182 cases of duodenal ulcer, were fatal.



THE DISTRIBUTION OF PATIENTS BY AGE AND SEX

Sex. Men comprised 62 per cent. (88 cases) of the gastric ulcer group and 72 per cent. (131 cases) of those with duodenal ulcers. This gave a male to female ratio of 1·6 to 1 for patients with gastric ulcers, and 2·6 to 1 for those with duodenal ulcers. These figures contrast with ratios for patients in London with non-bleeding gastric ulcers of 2·4 to 1, and with non-bleeding duodenal ulcers of 6·8 to 1 (Jones, 1952), and support the suggestion that peptic ulcers bleed more easily in women than in men (Baker, 1947; Norbye, 1952; Lambling, Bonfils, and Baratgin, 1957), although Ivy, Grossman, and Bachrach (1951) in their large review did not find this so. With minor exceptions, mortality was consistently higher among male patients (Table I).

Age. The ages of the patients ranged from 15 to 90 years, the proportion of men to women in most 10-year age groups being approximately the same as that for the whole group (see Figure). Of patients with duodenal ulcers 62 per cent., and of those with gastric ulcers 73 per cent., were over 50 years old. The

TABLE I

Mortality for Different Age and Sex Groups, and for All Patients

(Percentages shown in parentheses)

	Patients with gastric ulcers						*Patients with duodenal ulcers*					
	Male		*Female*		*Total*		*Male*		*Female*		*Total*	
Age (years)	*Number*	*Deaths*	*Number*	*Deaths*	*Number*	*Deaths*	*Number*	*Deaths*	*Number*	*Deaths*	*Number*	*Deaths*
All ages . . .	88	21 (24)	55	8 (15)	143	29 (20)	131	12 (9)	51	2 (4)	182	14 (8)
Under 51 . .	23	0	14	0	37	0	52	1* (2)	17	0	69	1 (1·4)
51 and over . .	65	21 (32)	41	8 (20)	106	29 (27)	79	11 (14)	34	2 (6)	113	13 (12)
51–60 . . .	26	5 (19)	16	1 (6)	42	6 (14)	37	3 (8)	17	0	54	3 (6)
61–70 . . .	25	11 (44)	14	3 (21)	39	14 (36)	23	3 (13)	6	0	29	3 (10)
71–80 . . .	10	3	6	1	16	4 (25)	16	3 (19)	8	2	24	5 (21)
81–90 . . .	4	2	5	3	9	5 (56)	3	2	3	0	6	2 (33)

* A patient suffering from chronic alcoholism, hepatic cirrhosis, and chronic nephritis.

peak age for duodenal ulcers was between 51 and 60 years, and for gastric ulcers between 51 and 70 years. Below 51 years of age (106 patients; 33 per cent. of all cases) there was one death (Table I). Over 50 years mortality was almost directly related to age, and in most age groups it was higher among patients with chronic gastric ulcers.

TABLE II

Mortality in relation to the Manifestation of Bleeding

(Percentages shown in parentheses)

	Total number of cases	*Haematemesis ± melaena*		*Melaena without haematemesis*	
		Number of cases	*Deaths*	*Number of cases*	*Deaths*
Gastric ulcer .	143	106 (74)	19 (18)	37 (26)	10 (27)
Duodenal ulcer .	182	118 (65)	12 (10)	64 (35)	2 (3)
Total . .	325	224 (69)	31 (14)	101 (31)	12 (12)

TABLE III

The Relationship of Severity of Bleeding to Site of Ulcer

	Patients with gastric ulcers			*Patients with duodenal ulcers*			*All patients*		
	Male	*Female*	*Total*	*Male*	*Female*	*Total*	*Male*	*Female*	*Total*
Number of cases .	88	55	143	131	51	182	219	106	325
Degree of bleeding: percentage — Mild .	43	56	50	56	57	57	51	57	53
Degree of bleeding: percentage — Severe	57	44	50	44	43	43	49	43	47

The manifestation of bleeding (Table II). Haemorrhage from a gastric ulcer was more commonly manifested by haematemesis than by melaena alone. Seventy-four per cent. of patients with chronic gastric ulcers had haematemesis, in contrast to 65 per cent. of those with duodenal ulcers. Taking all the patients together, 69 per cent. were admitted with haematemesis. This agrees with the figure of 68 per cent. given by Ivy, Grossman, and Bachrach (1951) in their review of 1,026 recorded cases, but not with the series of Norbye (1952) in which only a little over one-third presented haematemesis. Our findings were unusual in that chronic gastric ulcer had a higher mortality (27 per cent.) with melaena alone than with haematemesis with or without melaena (18 per cent.).

Severity of bleeding was assessed from the history (often inaccurate), the clinical picture on admission, the evolution of the disorder in the ward, the level of the haemoglobin, the effect on the blood-pressure, and the amount of blood transfused. Blood was given if the patient was shocked, that is with a systolic blood-pressure below 85 mm. Hg for more than about half an hour, or if the haemoglobin was below 6·5 g. per 100 ml. (45 per cent.). Loss of blood has been classified simply as mild or severe in Table III, which also shows its relationship with the site of the ulcer and the sex. Our figures agree with the general finding that severe haemorrhage is commonest in male patients with chronic

gastric ulcers. The incidence of severe bleeding in both types of ulcer together was 47 per cent., which is higher than the figure of 35·6 per cent. given by Ivy, Grossman, and Bachrach (1951) in their review of 2,526 collected cases. It is known that many patients with mild gastroduodenal bleeding in the area served by this hospital are not sent for admission.

The length of ulcer history before bleeding. Ferguson and Wyman (1951) and Chinn and Weckesser (1951) found that patients with the shortest histories of dyspepsia had the highest mortality. Details of the length of history in our patients are given in Tables IV and V. Patients with a gastric ulcer were more

TABLE IV

Length of Ulcer History Before Bleeding, and Mortality

(Percentages shown in parentheses)

		Duration (years)					
		0–1		*1–5*		*Over 5*	
	Number of cases	*Number of cases*	*Deaths*	*Number of cases*	*Deaths*	*Number of cases*	*Deaths*
Gastric ulcer .	143	51 (36)	16 (31)	29 (20)	5 (17)	63 (44)	8 (13)
Duodenal ulcer .	182	32 (18)	6 (18)	42 (23)	4 (10)	108 (59)	4 (4)
Total . .	325	83 (26)	22 (26)	71 (22)	9 (13)	171 (53)	12 (7)

TABLE V

Patients with a Short Ulcer History, and their Mortality

(Percentages shown in parentheses)

		Duration (weeks)					
		0–1		*1–6*		*Over 6*	
	Number of cases	*Number of cases*	*Deaths*	*Number of cases*	*Deaths*	*Number of cases*	*Deaths*
Gastric ulcer .	51	21 (41)	11 (52)	13 (25)	1 (8)	17 (33)	4 (24)
Duodenal ulcer .	32	6 (19)	2 (33)	9 (28)	1 (11)	17 (53)	3 (18)
Total . .	83	27 (33)	13 (48)	22 (27)	2 (9)	34 (41)	7 (21)

likely to bleed early in their history than those with a duodenal ulcer, whatever their sex. There was a large proportion of patients, however, in both groups (about 60 per cent. of those with a duodenal ulcer), in whom bleeding first occurred after five years. The figures in Table IV indicate a general trend towards a higher mortality among patients with a short history of dyspepsia, especially among those with gastric ulcers. When patients with a history of one year or less are subdivided as in Table V, two further trends are suggested. First, patients with no previous history, or one of no more than seven days, had a very high mortality. Secondly, patients with the next highest mortality were those with a history of between six weeks and one year. Both trends were more marked in patients with gastric ulcers. These findings may be explained by the high incidence of severe associated disease in the patients with a dyspeptic

history of one week or less. That in many patients the high fatality rate was due to associated disease was suggested by the fact that of 11 patients, with less than a year's history of gastric ulcer, who were submitted to emergency surgery, none died, compared to a 40 per cent. fatality rate in this sub-group treated medically. In only one of the 11 surviving surgical patients was there severe associated disease. (This consideration may have influenced the resort to surgery.) Thus a very short ulcer history may not by itself be of grave import.

TABLE VI

The Effect of Previous Haematemesis or Melaena on Mortality

(Percentages shown in parentheses)

		No previous haemorrhage		*Previous haemorrhage*	
	Number of cases	*Number of cases*	*Deaths*	*Number of cases*	*Deaths*
Gastric ulcer .	143	112	26 (23)	31	3 (10)
Duodenal ulcer .	182	124	14 (11)	58	0
Total . .	325	236	40 (17)	89	3 (3·4)

TABLE VII

Mortality related to Recurrence of Bleeding after Admission

(Percentages shown in parentheses)

	No recurrence		*One recurrence*		*Two or more recurrences*	
	Number of cases	*Deaths*	*Number of cases*	*Deaths*	*Number of cases*	*Deaths*
Gastric ulcer .	84 (59)	13 (15)	43	9 (21)	16	7 (44)
Gastric ulcer treated surgically . .	6	2	18	1	8	0
Duodenal ulcer .	129 (71)	2 (1·6)	38	9 (24)	15	3 (20)
Duodenal ulcer treated surgically	4	1	10	3	8	1
Total . . .	213	15 (7)	81	18 (22)	31	10 (32)
Total treated surgically . .	10	3	28	4	16	1
Total of patients with one or more recurrences .			112 (34)	28 (25)		
Total of patients treated surgically			44	5 (11)		

History of previous bleeding. The effect of past haematemesis or melaena on mortality is shown in Table VI. Such a history has been found not to worsen the outlook (Baker, 1947; Lewison, 1950; Ferguson and Wyman, 1951; Fraenkel and Truelove, 1955); indeed, among our cases it improved it, for patients who had not bled before fared worse than those who had, and this was so whether the source of haemorrhage was a gastric or a duodenal ulcer. It is clear that a history of bleeding in the past is not by itself a criterion for emergency surgery.

Continued bleeding after admission to hospital. It has long been recognized

that bleeding which continues or recurs after admission to hospital is a grave sign (Cullinan and Price, 1932; Burger and Hartfall, 1934; Jones, 1943, 1947; Gordon-Taylor, 1945; Baker, 1947; Needham and McConachie, 1950; Chinn and Weckesser, 1951). As Jones (1956) has shown, it carries a worse prognosis when it comes from a chronic ulcer than from an acute lesion. There was among our patients a higher incidence of continued or recurrent bleeding (41 per cent. for gastric ulcers; 29 per cent. for duodenal ulcers; Table VII) than that found by Jones (1956). It was mainly in these cases that surgical intervention took place. A few patients without recurrent bleeding were treated by surgery because of perforation, massive haemorrhage at home, a large haemorrhage while in the wards for another condition, or repeated past bleeding in a patient known to have a gastric ulcer. If bleeding took place after admission to hospital, mortality was high. Among patients with gastric ulcers, more died after two or more recurrences than after one, but this trend was not apparent in patients with duodenal ulcers. Operative success was greatest in cases of recurrent bleeding from chronic gastric ulcers, only one out of 26 patients being lost. The mortality for the gastric ulcer group as a whole was 27 per cent. The results of surgical treatment in patients with duodenal ulcers was more disappointing. Even so there was only one death among eight patients with two or more recurrences of bleeding who were submitted to surgery. The fatality rate was 25 per cent. for all patients with recurrent bleeding, but only 11 per cent. for those treated surgically. The findings suggest the importance of considering surgery early in patients with chronic peptic ulcer, especially gastric ulcer, who bleed after admission to hospital.

Association of bleeding with perforation. The adage that haemorrhage and perforation do not occur together has been disproved. Winters and Egan (1939) found bleeding in 10 per cent. of 361 patients admitted for perforation of a peptic ulcer. Jones (1956) reported 11 patients with perforation after admission for bleeding, of whom five were undiagnosed and six died, and 38 patients who bled after admission for perforation, of whom 17 died. The two conditions occurred together in nine of our patients (eight with gastric ulcers). Seven patients died. Three were admitted for perforated ulcers, and bled afterwards; in the others bleeding preceded perforation. There was one survivor in each group. Two were treated successfully and two unsuccessfully by operation, one refused surgery, and four were diagnosed at autopsy.

Observations on the venous pressure. The venous pressure falls during bleeding, and if the haemorrhage is large enough, or continues, the blood-pressure also falls (McMichael, 1944; Barcroft, Edholm, McMichael, and Sharpey-Schafer, 1944; Howarth, McMichael, and Sharpey-Schafer, 1946). At this stage transfusion is safe and, if adequate, will raise the blood-pressure (Howarth and Sharpey-Schafer, 1947). Sharpey-Schafer (1944, 1945) has shown that in anaemia from any cause the right auricular pressure may eventually become raised, with an associated increase in cardiac output and a sustained blood-pressure. Howarth and Sharpey-Schafer (1947) showed that after gastrointestinal haemorrhage this hyperdynamic state might finally be associated with a low blood-pressure

history of one week or less. That in many patients the high fatality rate was due to associated disease was suggested by the fact that of 11 patients, with less than a year's history of gastric ulcer, who were submitted to emergency surgery, none died, compared to a 40 per cent. fatality rate in this sub-group treated medically. In only one of the 11 surviving surgical patients was there severe associated disease. (This consideration may have influenced the resort to surgery.) Thus a very short ulcer history may not by itself be of grave import.

TABLE VI

The Effect of Previous Haematemesis or Melaena on Mortality

(Percentages shown in parentheses)

		No previous haemorrhage		*Previous haemorrhage*	
	Number of cases	*Number of cases*	*Deaths*	*Number of cases*	*Deaths*
Gastric ulcer	143	112	26 (23)	31	3 (10)
Duodenal ulcer	182	124	14 (11)	58	0
Total	325	236	40 (17)	89	3 (3·4)

TABLE VII

Mortality related to Recurrence of Bleeding after Admission

(Percentages shown in parentheses)

	No recurrence		*One recurrence*		*Two or more recurrences*	
	Number of cases	*Deaths*	*Number of cases*	*Deaths*	*Number of cases*	*Deaths*
Gastric ulcer	84 (59)	13 (15)	43	9 (21)	16	7 (44)
Gastric ulcer treated surgically	6	2	18	1	8	0
Duodenal ulcer	129 (71)	2 (1·6)	38	9 (24)	15	3 (20)
Duodenal ulcer treated surgically	4	1	10	3	8	1
Total	213	15 (7)	81	18 (22)	31	10 (32)
Total treated surgically	10	3	28	4	16	1
Total of patients with one or more recurrences			112 (34)	28 (25)		
Total of patients treated surgically			44	5 (11)		

History of previous bleeding. The effect of past haematemesis or melaena on mortality is shown in Table VI. Such a history has been found not to worsen the outlook (Baker, 1947; Lewison, 1950; Ferguson and Wyman, 1951; Fraenkel and Truelove, 1955); indeed, among our cases it improved it, for patients who had not bled before fared worse than those who had, and this was so whether the source of haemorrhage was a gastric or a duodenal ulcer. It is clear that a history of bleeding in the past is not by itself a criterion for emergency surgery.

Continued bleeding after admission to hospital. It has long been recognized

that bleeding which continues or recurs after admission to hospital is a grave sign (Cullinan and Price, 1932; Burger and Hartfall, 1934; Jones, 1943, 1947; Gordon-Taylor, 1945; Baker, 1947; Needham and McConachie, 1950; Chinn and Weckesser, 1951). As Jones (1956) has shown, it carries a worse prognosis when it comes from a chronic ulcer than from an acute lesion. There was among our patients a higher incidence of continued or recurrent bleeding (41 per cent. for gastric ulcers; 29 per cent. for duodenal ulcers; Table VII) than that found by Jones (1956). It was mainly in these cases that surgical intervention took place. A few patients without recurrent bleeding were treated by surgery because of perforation, massive haemorrhage at home, a large haemorrhage while in the wards for another condition, or repeated past bleeding in a patient known to have a gastric ulcer. If bleeding took place after admission to hospital, mortality was high. Among patients with gastric ulcers, more died after two or more recurrences than after one, but this trend was not apparent in patients with duodenal ulcers. Operative success was greatest in cases of recurrent bleeding from chronic gastric ulcers, only one out of 26 patients being lost. The mortality for the gastric ulcer group as a whole was 27 per cent. The results of surgical treatment in patients with duodenal ulcers was more disappointing. Even so there was only one death among eight patients with two or more recurrences of bleeding who were submitted to surgery. The fatality rate was 25 per cent. for all patients with recurrent bleeding, but only 11 per cent. for those treated surgically. The findings suggest the importance of considering surgery early in patients with chronic peptic ulcer, especially gastric ulcer, who bleed after admission to hospital.

Association of bleeding with perforation. The adage that haemorrhage and perforation do not occur together has been disproved. Winters and Egan (1939) found bleeding in 10 per cent. of 361 patients admitted for perforation of a peptic ulcer. Jones (1956) reported 11 patients with perforation after admission for bleeding, of whom five were undiagnosed and six died, and 38 patients who bled after admission for perforation, of whom 17 died. The two conditions occurred together in nine of our patients (eight with gastric ulcers). Seven patients died. Three were admitted for perforated ulcers, and bled afterwards; in the others bleeding preceded perforation. There was one survivor in each group. Two were treated successfully and two unsuccessfully by operation, one refused surgery, and four were diagnosed at autopsy.

Observations on the venous pressure. The venous pressure falls during bleeding, and if the haemorrhage is large enough, or continues, the blood-pressure also falls (McMichael, 1944; Barcroft, Edholm, McMichael, and Sharpey-Schafer, 1944; Howarth, McMichael, and Sharpey-Schafer, 1946). At this stage transfusion is safe and, if adequate, will raise the blood-pressure (Howarth and Sharpey-Schafer, 1947). Sharpey-Schafer (1944, 1945) has shown that in anaemia from any cause the right auricular pressure may eventually become raised, with an associated increase in cardiac output and a sustained blood-pressure. Howarth and Sharpey-Schafer (1947) showed that after gastrointestinal haemorrhage this hyperdynamic state might finally be associated with a low blood-pressure

(their 'low blood-pressure phase 3'). This is a serious condition. It is difficult to treat because of the danger of overloading the heart, for transfusion is hazardous when the venous pressure is raised. Fortunately the condition is relatively rare.

TABLE VIII

Patients with a Raised Venous Pressure at Different Ages

Age	*21–30*	*31–40*	*41–50*	*51–60*	*61–70*	*71–80*	*81–90*	*Total*
Number of patients	2	2	5	10	13	7	2	41
Deaths . . .	0	0	0	5 (2 with perforation)	6	4	1	16 (39%)
'Low blood-pressure phase 3' (Howarth and Sharpey-Schafer, 1947) . . .	..	1 (mitral stenosis)	..	5	5	4	1	16
Deaths . . .	..	0	..	3	4	4	1	12 (75%)

TABLE IX

The Effect of Increased Venous Pressure on Prognosis and Treatment

(Percentages shown in parentheses)

	Medical treatment		*Surgical treatment*	
Jugular venous pressure	*Number of cases*	*Deaths*	*Number of cases*	*Deaths*
(*a*) Normal on admission and remaining normal . .	223	19 (9)	47	6 (13)
(*b*) Raised on admission. . .	19	8	3	2
(*c*) Normal on admission and becoming raised	10	5	9	1
(*b*)+(*c*)	29	13 (45)	12	3 (25)

Data relating to the state of the venous pressure were available in 311 cases. The diagnosis of a hyperdynamic cardiovascular state was made clinically by the finding of warm hands, a high pulse-pressure, and raised jugular venous pressure. In the recumbent or semi-recumbent position the normal level of the jugular venous pressure was taken as 4 to 5 cm. below the sternal angle. On this basis it was increased in 41 patients (13 per cent.), 28 with gastric and 13 with duodenal ulcers (Table VIII). In 22 of the patients the venous pressure was raised on admission, and in 19 it increased afterwards, usually during blood transfusion (Table IX). Although age might be expected to be an important factor in determining the manner in which the cardiovascular system responds to haemorrhage and anaemia, patients with a raised venous pressure were not confined to the elderly, and their ages ranged from 21 to 82 years

(Table VIII). Seventy-eight per cent., however, were aged 51 years or more, and over half (54 per cent.) 61 or more. Among these 41 cases there were 16 in the 'low blood-pressure phase 3' of Howarth and Sharpey-Schafer (1947) (Table VIII). Thus this state was seen only once or twice a year with this type of peptic ulcer. Three patients were included in whom the blood-pressure fell from hypertensive to low normal levels. Frank congestive heart failure with peripheral oedema and, in one case, enlargement of the liver, appeared in seven patients. It might have been commoner but for the dehydration and salt loss that result from haemorrhage. The jugular venous pressure was usually raised to the level of, or to 1 or 2 cm. above, the sternal angle, but it tended to be higher in patients who were in 'low blood-pressure phase 3'. Disease of the heart was found in 37 of 270 patients without venous congestion (14 per cent.) and in 20 of the 41 patients with venous congestion. It was present in 13 of the 22 patients (59 per cent.) in whom venous congestion was found on admission, but in only seven of the 19 (37 per cent.) in whom venous congestion appeared later. Nine patients suffered from chronic bronchitis and emphysema of such degree as to affect the heart; six had benign, and one malignant, hypertension; three suffered from ischaemic heart disease; one each had: syphilitic aortic aneurysm and aortic incompetence; aortic stenosis; mitral stenosis; septic pericarditis; auricular fibrillation. Two forms of heart disease were present in each of four patients. Cardiac disorder was commonest among patients in 'low blood-pressure phase 3', and occurred in 11 of the 16 in this group. Of the 41 patients with a raised venous pressure 16 (39 per cent.) died, their ages ranging from 51 to 81 years (Table VIII). Twelve (75 per cent.) of the 16 patients in 'low blood-pressure phase 3' died. Their ages ranged from 56 to 81 years, and five were aged 71 or over. In all but one of these 12 patients who died associated factors probably contributed to death, for example: overwhelming haemorrhage; perforation; cor pulmonale; recent cardiac infarction; benign or malignant hypertension; emphysema and bronchopneumonia; cirrhosis of the liver; diabetes mellitus and myocardial fibrosis; aortic stenosis and post-operative peritonitis; subphrenic abscess, empyema, and septic pericarditis.

Of the 29 patients with raised venous pressure treated medically 13 (45 per cent.) died (Table IX). Two of the three patients admitted with a raised venous pressure who came to surgery died. In contrast, of the nine patients (seven with gastric ulcers) whose venous pressure rose after admission, and who were submitted to surgery, only one died. This patient was aged 69, and developed peritonitis after the operation. The ages of the eight survivors ranged from 34 (a patient with mitral stenosis, the only one with associated disease of importance) to 82. Three of these patients (including the fatal case) were in 'low blood-pressure phase 3'.

In sum, with medical treatment the fatality rate for patients without venous congestion was 9 per cent., and for patients with congestion 45 per cent. (Table IX). These figures contrast with the fatality rate of 13 per cent. for all medically treated cases (Table X). With surgical treatment the fatality rate for patients without venous congestion was 13 per cent., and for patients with

congestion 25 per cent. (Table IX). These figures contrast with the fatality rate of 15 per cent. for all surgically treated patients (Table X). In patients with a raised venous pressure there was no special relation between the level of the haemoglobin and either low blood-pressure or mortality.

Treatment. All patients first received standard medical treatment, with early feeding, and transfusion of blood as required. Particular attention was paid to the state of hydration. Patients lose much fluid after haemorrhage by sweating, and by diuresis from extrarenal uraemia. Dehydration is a common cause of

TABLE X

Mortality among Patients, Classified by Sex and Type of Ulcer, Receiving Different Treatments

(Percentages shown in parentheses)

	Sex	Total number of cases	Medical treatment		Emergency surgical treatment		Total deaths
			Number of cases	Deaths	Number of cases	Deaths	
Gastric ulcer	M	88	64	18 (28)	24	3 (12)	21 (24)
	F	55	47	8 (17)	8	0	8 (15)
	M+F	143	111	26 (23)	32 (22)	3 (9)	29 (20)
Duodenal ulcer	M	131	113	8 (7)	18	4 (22)	12 (9)
	F	51	47	1 (2)	4	1 (25)	2 (4)
	M+F	182	160	9 (6)	22 (12)	5 (23)	14 (8)
Total	M	219	177	26 (15)	42	7 (17)	33 (15)
	F	106	94	9 (10)	12	1 (8)	10 (9)
	M+F	325	271 (83)	35 (13)	54 (17)	8 (15)	43 (13)

hypotension. If the venous pressure was raised intravenous digoxin (1·0 to 1·5 mg.) was given at once. This normally controlled the venous pressure, and enabled further blood to be transfused. Whenever recurrent or continuing bleeding occurred in the ward, and before in a few cases, a surgeon saw the patient without delay, and subsequent treatment was decided jointly. When bleeding was of such a degree that the patient's life was thought to be in peril, partial gastrectomy was attempted, provided the operation itself would not obviously hasten death. Minor factors influencing the decision towards surgery were the suspicion of gastric carcinoma, and the patient's possession of a rare blood group. Fifty-four patients (17 per cent. of the whole series) were submitted to emergency surgery, that is, operation during bleeding or within 48 hours of its cessation (Table X). Thirty-two of these had gastric ulcers, and 22 duodenal ulcers. These proportions, 22 per cent. and 12 per cent. of the respective ulcer groups, are comparable with those given in the series of Jones (1956) (18·8 per cent. and 9·5 per cent. respectively). A partial gastrectomy was performed in 50 patients, but was impossible in four for technical reasons. In two of these four the bleeding vessel was ligatured and the ulcer sutured, a gastroenterostomy being performed in one case. In the other two nothing was done. All other patients, including those submitted to surgery later (a considerable number) were classified as receiving medical treatment.

The mortality among patients with gastric ulcers was 20 per cent., but with medical treatment it was 23 per cent., compared to 9 per cent. in those submitted to surgery. Of the patients with duodenal ulcers 8 per cent. died, but with medical treatment the mortality was 6 per cent. compared to 23 per cent. after surgery. The mortality among all patients receiving medical treatment was 13 per cent., and in those submitted to emergency surgery 15 per cent. The fatality rate for all the patients together was 13 per cent. Analysis of mortality in respect of age as well as treatment (Table XI) shows that between 51 and 60 years of age 18 per cent. of patients with gastric ulcers died under medical treatment, whereas of eight submitted to surgery all survived. Further, in patients with gastric ulcers who were over 60 years of age, the mortality after surgery (20 per cent.) was half that with medical treatment. On the other hand, elderly patients with duodenal ulcers fared badly under surgery, four out of eight dying. Women of all ages did well with surgery, all but one of 12 surviving (Table X). The mortality among male patients with surgery was twice as high (17 per cent.).

TABLE XI

Mortality related to Age and Treatment

(Percentages shown in parentheses)

	Patients with gastric ulcers				*Patients with duodenal ulcers*			
	Medical treatment		*Emergency surgical treatment*		*Medical treatment*		*Emergency surgical treatment*	
Age (years)	*Number of cases*	*Deaths*	*Number of cases*	*Deaths*	*Number of cases*	*Deaths*	*Number of cases*	*Deaths*
< 51 . .	28	0	9	0	61	1 (1·6)	8	0
51–60 . .	34	6 (18)	8	0	48	2 (4)	6	1 (17)
61–70 . .	27	11 (41)	12	3 (25) } (20)	25	2 (8) } (12)	4	1 (25) } (50)
71 and over .	22	9 (41)	3	0 }	26	4 (15) }	4	3 (75) }

Miscellaneous factors possibly influencing the results of surgery. In the past evidence has indicated that the risk of emergency surgery was greater in patients who suffered delay or repeated haemorrhages (Gordon-Taylor, 1935; Finsterer, 1939; Maingot, 1941; Heuer, 1946; Lewison, 1950; Chinn and Weckesser, 1951; Weber, Schroeter, and Riddell, 1958). Whether this need always be true has been questioned (Gordon-Taylor, 1945; *Lancet*, 1950). Data concerning various relevant factors for our patients submitted to surgery, shown separately for survivors and for those who died, are given in Table XII. They include the duration of the haemorrhage before admission, the time in the ward before operation, these two periods added together, the severity of the haemorrhage, the number of attacks of hypotension recorded (blood-pressure below 100 mm. Hg systolic), associated diseases considered likely to affect the prognosis, the lowest haemoglobin concentration recorded, and the amount of blood transfused before operation. The data show that these factors were no more numerous among those who died than among the survivors. Indeed there were a number of recoveries among patients who had been bleeding severely over a long period,

TABLE XII

Factors, Possibly Adverse, in Patients Submitted to Surgery

Outcome	*Number of patients*	*Duration of bleeding before admission (days) (a)*	*Time in ward before operation (days) (b)*	*(a)+(b) (days)*	*Severity of haemorrhage*	*Attacks of hypotension recorded*	*Associated diseases*	*Lowest haemoglobin level recorded (%)*	*Pre-operative blood transfusion (pints)*
Patients with gastric ulcers									
Alive	29	0–28 Av. 3·7	0·5–22 Av. 4·5	1–30 Av. 8·1	Mild 2 Severe 27	None 7 One 13 Two 7 Three 2	None 23 One 4 Two 2	26–86 Av. 52	0–20 Av. 8
Dead	3	4 hours	0·5	16 hours	Severe	One	One	66	4
		3 days	3	6 days	,,	One	One	47	17
		28 days	9	37 days	,,	None	One	38	3
Patients with duodenal ulcers									
Alive	17	0–14 Av. 2	1–18 Av. 3·9	1–25 Av. 6	Mild 1 Severe 16	None 3 One 6 Two 5 Three 3	None 12 One 4 Two 1	28–93 Av. 52	0–15 Av. 8
Dead	5	0·5	1	1·5	Severe	Two	Two	65	13
		0·5	1	1·5	,,	Two	Four	57	9
		0·5	2	2·5	,,	One	None	43 Av. 48	8 Av. 8
		2	0·5	2·5	,,	One	None	32	3
		2	13	15	,,	One	None	43	8

and among several with repeated attacks of hypotension who had received numerous blood transfusions. Among patients who died, delay in operating was less than the average in all but two. Patients with duodenal ulcers were submitted to surgery more quickly than those with gastric ulcers, but had a higher mortality. Associated diseases occurred among the survivors, and were absent in some who died. The level of the haemoglobin bore no relation to prognosis.

TABLE XIII

The Main Causes of Death in Patients who Died

Haemorrhage	11 patients	(one in 'low blood-pressure phase 3')
Haemorrhage and associated disease	11 ,,	
'Low blood-pressure phase 3'	10 ,,	(one with post-operative peritonitis)
Perforation	7 ,,	(one in 'low blood-pressure phase 3')
Post-operative peritonitis	1 patient	
Collapse at end of operation	1 ,,	
Collapse (? cause)	1 ,,	(aged 90)
Unknown, after operation	1 ,,	
Total	43 patients	

Causes of Death

The probable reasons why patients died are listed in Table XIII. The commonest principal causes of death were overwhelming haemorrhage, associated diseases, low blood-pressure with a hyperdynamic circulation, and perforation. Associated diseases considered to have been mainly responsible for a fatal outcome after the haemorrhage (with the patients' ages) were as follows: carcinoma of bronchus with generalized metastases, including ulcerated metastases in the stomach (64); syphilitic aortitis with aortic valve incompetence and aneurysm (65); syphilitic aortic aneurysm and tabes dorsalis (60); carcinoma of bronchus with metastases in the liver and suprarenal glands (51); bronchopneumonia, pyelonephritis, and parotitis (81); chronic bronchitis, emphysema, pneumonia, and congestive heart failure (51); malignant hypertension (54); chronic alcoholism, cirrhosis of the liver, and chronic nephritis (43); post-operative pulmonary embolism and bronchopneumonia (82); cardiac infarction (80); ileus leading to peritonitis without overt perforation, and bronchopneumonia (74). The causes of death in patients who died after operation were considered to be: subphrenic abscess after perforation (two cases) (in one the perforation was sutured before the patient began to bleed, and he is not therefore included among those surgically treated for bleeding); 'low blood-pressure phase 3' (two cases); post-operative haemorrhage (one case); associated diseases (one case); post-operative peritonitis (one case); collapse at the end of operation (one case); unknown (one case).

Discussion

Relatively few authors have dealt specifically with chronic ulcers in the stomach and duodenum, or given data about them separately. The overall

mortality of 20 per cent. for our patients with bleeding chronic gastric ulcers, and of 8 per cent. for those with bleeding duodenal ulcers, compares with 16·7 per cent. among 1,080 patients with gastric ulcers and 8·8 per cent. among 2,150 patients with duodenal ulcers collected by Ivy, Grossman, and Bachrach (1951). The greater mortality in our patients with gastric ulcers may be explained partly by the high incidence of severe bleeding, and partly by the exclusion of patients with acute erosions. Needham and McConachie (1950) and Jones (1947, 1952) showed that bleeding from such erosions carries a mortality about six times less than that from chronic gastric ulcers. Ferguson and Wyman (1951) reported a mortality of 36·5 per cent. among 49 cases of bleeding chronic gastric ulcers, and of 10·4 per cent. among 48 cases of duodenal ulcer. Jones (1952) found a mortality of 19 per cent. among 231 patients with chronic gastric ulcers, and of 8 per cent. among 379 with duodenal ulcers. In the present series mortality was higher in each age group among patients with gastric ulcers. These differences probably arise from the fact that gastric ulcers commonly bleed more severely than duodenal ulcers. Our results show that bleeding was more severe and most likely to be fatal if the patient was a man over 60 years of age with a chronic *gastric* ulcer. This is in accordance with the findings of other authors. Our patients with gastric ulcers were more likely to die if bleeding was manifested by melaena alone. Perhaps, as Jones (1947) suggested, such patients are sometimes too weak to vomit. The innocuousness of repeated haemorrhage in the past contrasts strangely with the evil results of continued or recurrent bleeding in the ward. The association—not so rare as was once thought—of perforation with bleeding is especially dangerous, and early operation is essential. It is often difficult to diagnose, but the condition is suggested by pain which continues after bleeding. There were no special pointers to the diagnosis in our patients. Two collapsed suddenly and died rapidly. The subject is discussed briefly by Ivy, Grossman, and Bachrach (1951).

Associated disease must worsen the prognosis in the individual patient, but in a series of cases it is difficult to interpret its significance. A number of patients who recovered suffered from several diseases. In some the bleeding ulcer (usually in the stomach) made its appearance late in the history of previously existing disorders. A number of authors, among them Jones (1943) and Chinn and Weckesser (1951), have believed that associated diseases are important factors increasing mortality. Examination of our cases with a short ulcer history suggested that the association of a high mortality might be mainly due to the presence of other debilitating conditions.

The original work of Sharpey-Schafer on cardiovascular complications of gastroduodenal haemorrhage has been mentioned. Sarnoff, Case, Waithe, and Isaacs (1954) showed that in dogs hypotension caused a reduced blood-flow through the coronary arteries, which resulted in a rise in left, and later right, auricular pressure; and cardiac dilatation occurred. Melcher and Walcott (1951) demonstrated myocardial damage in dogs from such hypotension.

Our patients in whom the venous pressure became raised suffered a considerably increased mortality (39 per cent.). Of those whose blood-pressure fell

in addition ('low blood-pressure phase 3') three-quarters died. Assessment of the cardiovascular state is therefore an important factor in prognosis. Patients whose venous pressure was raised on admission fared worse than those in whom it became raised afterwards. Heart disease was present in more of the former than the latter, and was found in half of all the patients with a raised jugular venous pressure. This suggests that venous congestion after haemorrhage may be an indication of cardiac disorder, and its early appearance a sign of the severity of this disorder. (Of course, associated disease was more likely to be found in patients who died and were subjected to autopsy). The fact that patients in whom venous congestion was of relatively short duration fared well after surgery showed that emergency operation is not necessarily barred by this finding. It was of interest that patients with congestion submitted to surgery did relatively better than those treated medically, their respective fatality rates being 45 per cent. and 25 per cent. Indeed surgery may be life-saving, for such patients tolerate further bleeding and transfusion badly, and the best course is to stop the haemorrhage. After preliminary treatment with digoxin, operation should be performed without delay. Even when the blood-pressure falls in the presence of venous congestion, surgery may help. Of four patients in 'low blood-pressure phase 3' submitted to surgery, two survived. Treatment of anaemia in the presence of venous congestion is difficult. In spite of the watch for venous congestion, prompt treatment with digoxin, which usually reduced it, and care over blood transfusions, the high mortality in patients with a raised jugular venous pressure indicated that medical treatment of venous congestion after haemorrhage could be improved.

Hypotension, with a systolic blood-pressure below about 80 mm. Hg, reduces blood-flow through the liver, resulting in hypoxia. This is brought about by a lowered portal blood-flow due, at least in part, to a reduction in splanchnic blood-flow (McMichael, 1937; Engel, Harrison, and Long, 1944; Reynell, 1954; Reynell, Marks, Chidsey, and Bradley, 1955), although this is partly offset by an increase in blood-flow through the spleen and hepatic artery (Grayson, 1954; Ginsburg and Grayson, 1954; Grayson and Mendel, 1957). These compensating mechanisms start to fail when the arterial systolic pressure falls below 80 mm. Hg (Grayson and Mendel, 1957). Liver damage due to anoxia has been demonstrated in animals in shock from haemorrhage (Russell, Long, and Wilhelmi, 1944), and if shock continues the damage may become irreversible, leading to the death of the animal (Engel, Harrison, and Long, 1944; Frank, Seligman, and Fine, 1946). Venous congestion may itself lead to diminished blood-flow through the liver, thus aggravating hepatic hypoxia. These factors may account in part for the high mortality in patients in 'low blood-pressure phase 3'. Prompt blood transfusion is obviously desirable in oligaemic hypotensive states, provided there is no venous congestion. It will prevent irreversible hepatic damage, and it is possible that it may also prevent the onset of venous congestion, especially when the heart is already disordered. Rapid transfusion, so long as the venous pressure remains low, is better than drip transfusion. Unthinking adherence to the 'drip' has undoubtedly resulted in blood sometimes being

given too slowly. The life-saving potentiality of transfusion, adequate in quantity and speed, has been demonstrated by Grant and Reeve (1951) in patients with loss of blood after war wounds.

Emergency surgery for massive gastroduodenal bleeding always carries a considerable risk. In his review of 805 collected emergency operations for such bleeding Crohn (1953) found 81 deaths (10 per cent.). There are few published series in which the results of medical treatment and of emergency surgery are given separately for patients with chronic gastric and duodenal ulcers. The criteria for emergency surgical intervention in patients with bleeding peptic ulcers are by no means settled. It is generally agreed that recurrent bleeding after admission worsens the prognosis. This, and the size and persistence of haemorrhage, were the main factors on which the need for emergency surgery was judged in our cases. Variations in the way in which treatment has been applied makes it difficult to compare its results in different series. The relevant reports are grouped in Table XIV into those in which the criteria for operation were different (part A), and those in which these criteria were similar, to those in our series (part B). The first group contains a small series (Bohn, 1949), a larger one reported by Stewart, Cosgriff, and Gray (1956), and a very large one collected at St. James' Hospital, Balham, during the years 1945 to 1958, the details of which have been kindly supplied by Mr. N. C. Tanner, Mr. A. M. Desmond, and Dr. B. F. A. Swynnerton. Apart from being by far the largest ever recorded, this single series of patients includes a remarkably high proportion of patients over 50 years of age. The results are all the more noteworthy. In these three series early operation was performed in the majority of cases as therapeutic policy, and not always within 48 hours of bleeding (Stewart, Cosgriff, and Gray, 1956). In the Balham series procedures other than partial gastrectomy were often performed (Tanner, 1950, 1954), and patients with perforations were excluded. In these reports there was little difference, as regards the results of surgery, between patients with gastric and duodenal ulcers, but patients treated medically had a lower mortality if they suffered from duodenal ulcers. Part B of Table XIV shows the series of cases in which emergency surgery was undertaken as an immediate life-saving measure in individual patients, and not as a matter of general therapeutic policy. Two series were small (Chinn and Weckesser, 1951; Snyder and Berne, 1957). Our results were similar to those of Jones (1956), with whose series ours is most closely comparable. Many factors must have operated to influence the mortality of patients in these different series. It is difficult to explain why patients with duodenal ulcers fared worse with surgery than patients with gastric ulcers in some series, but not in all. The greater technical difficulty, if it exists, of dealing with a bleeding duodenal ulcer would be a factor in all cases. The reports grouped in part B of Table XIV, in which this trend was notable, contained patients who were more likely to be severely ill, and this may have been a factor. It is difficult to understand why in most series patients with duodenal ulcers had a lower mortality with medical treatment than with emergency surgery. In our experience women responded particularly well to surgery.

TABLE XIV

Results of Emergency Surgical Treatment in Various Series of Patients

(Percentages given in parentheses)

Author	Number of cases		Emergency surgery		Partial gastrectomy		Deaths after operation		Deaths after medical treatment	
	G.U.	D.U.	G.U.	D.U.	G.U.	D.U.	G.U.	D.U.	G.U.	D.U.
A										
Bohn (1949)	39	41	16 (41)	8 (20)	? 16	? 8	2 (13)	0	7 (30)	1 (3)
Stewart, Cosgriff, and Gray (1956)	?	?	60	81	Most	Most	9 (15)	7 (9)	..	..
Tanner, Desmond, and Swynnerton (1959) — All cases	598	615	254 (42)	176 (29)	233	162	39 (15)	27 (15)	50 (14·5)	23 (5)
Tanner, Desmond, and Swynnerton (1959) — Patients aged 50 and over	434	344	196 (45)	122 (35)	180	110	36 (18)	26 (21)	48 (20)	23 (10)
B										
Chinn and Weckesser (1951)*	62	244	11 (18)	13 (5·5)	9	11	3 (27)	4 (31)	17 (27)	22 (9)
Jones (1956)	233	432	44 (19)	41 (9·5)	43	39	6 (14)	14 (32)	28 (15)†	22 (6)†
Snyder and Berne (1957)	14	59	10 (71)	10 (17)	7	7	2 (20)	2 (20)	3 (75)	6 (12)
Present series	143	182	32 (22)	22 (12)	30	20	3 (9)	5 (23)	26 (23)	9 (6)

G.U. = gastric ulcer. *D.U.* = duodenal ulcer.

* Ulcers probably mostly chronic.

† Figures obtained by personal communication.

A Emergency operation performed readily, as general therapeutic policy.

B Emergency operation performed mainly to save the life of individual patients.

Delay in operating, which occurred with some of our patients, was due to several reasons. Associated disease was a common cause of reluctance to operate. There is also a natural hesitation to submit a patient to surgery within a few hours of his first haemorrhage in the absence of a dyspeptic history. Yet such a patient may well have a large gastric ulcer, with a poor prognosis, and the evidence suggests that the outlook can be improved by emergency surgery. The fact that our patients who suffered delay and repeated haemorrhages before operation fared no worse, on the whole, than those brought quickly to surgery suggests that methods of resuscitation and medical treatment, as well as surgical skill, are better than in the past. This may be particularly true of the treatment of hypotension and venous congestion. Nevertheless surgery, if it is to be undertaken to stop bleeding, should be done as early as possible. Our experience suggests that associated diseases are not necessarily a bar to emergency surgery. Bleeding was sometimes so rapid and massive that surgery was not possible, the patient dying out of hand. Such patients, shown as treated medically, thus weighted the mortality figures for medical treatment.

That it is important to discover the site and source of bleeding quickly is indicated by consideration of the various prognostic factors discussed, and in particular by the good results of emergency surgery which may be obtained in patients with recurrent bleeding from chronic gastric ulcers. The means of diagnosis available are discussed below.

Methods of Diagnosis

We shall assume that the diagnosis has been narrowed to some form of peptic ulceration as a cause of the haemorrhage. The clinical history may suggest the site of the ulcer, but the story is often misleading. Bleeding after a short history of dyspepsia is commoner with a gastric ulcer, but nearly one-fifth of our duodenal ulcer patients bled within a year of the onset of dyspepsia, and bleeding was commoner in gastric ulcer patients after five years' dyspepsia than in those with a history of less than one year (Table IV). Ancillary methods are needed for accurate diagnosis. They entail certain X-ray and laboratory facilities, and adequate medical and nursing staff.

Barium-meal examination. There are contradictory reports of the value and safety of a barium meal when performed during or immediately after a haemorrhage, even with the non-manipulative Hampton (1937) technique. Some authors have found it useful and safe (Amendola, 1949; Elmer, Rousuck, and Ryan, 1950; Alsobrook, Schell, and McCleery, 1952; Knowles, Felson, Shapiro, and Schiff, 1952; Zamchek, Chalmers, Ritvo, and Osborne, 1952; Mayo and Owens, 1954; Aldman and Wallensten, 1956; Schatzki and Blade, 1958). Others have thought it dangerous (Crohn and Janowitz, 1951; Jones, 1956). We have only occasionally made use of this method.

Hourly measurements of gastric juice pH. Chandler and Watkinson (1953 and 1959) measured the pH of gastric juice aspirated hourly from patients who had bled. They found the results of diagnostic value in 152 (85 per cent.) of 179

patients in whom the secretion pattern was abnormal. High nocturnal acidity was noted in 57 of 68 patients with duodenal ulcers, nocturnal neutralization in 26 of 33 patients with gastric ulcers, and achlorhydria in 69 of 78 patients with acute ulcers. Although blood in the stomach may reduce the acidity of gastric juice by a buffering effect (Schneider, 1957), in practice this is a useful method in helping to locate the ulcer.

TABLE XV

Results of Gastroscopy in Cases of Gastroduodenal Bleeding (Central Middlesex Hospital, 1952–1956)

(By courtesy of Dr. F. Avery Jones and Dr. Donald Kellock)

Final diagnosis	*Number of patients examined*	*Failed or incomplete examination*	*No abnormality found*	*Ulcer seen*	*Mamillation of gastric mucosa*
Chronic gastric ulcer . .	54	7	1	46	0
Duodenal ulcer .	85	13	56	..	16
Acute gastric lesion	51	3	4	43	1
Total . . .	190	23 (12%)	61	89	17
				167* (88%)	

* Diagnosis incorrect in six instances (3·6%).

Estimation of pepsinogen in blood and urine. Groups of patients with duodenal ulcers have higher average levels of pepsinogen in their blood than are found in groups of patients with gastric ulcers or other lesions causing similar bleeding (Hirschowitz, 1955; Hoar and Browning, 1956). Unfortunately there is a wide scatter among individual patients, with much overlapping of results (Mirsky, Fisher, and Harbison, 1955; Spiro, Ryan, and Jones, 1955). The same remarks apply to the amounts of pepsinogen found in urine (Hirschowitz, 1953; Mackenzie, 1953; Sircus, 1954; Gray, Ramsey, and Reifenstein, 1954; Segal, Miller, Reichsman, Plumb, and Glaser, 1957). We have no experience of this test, for it has not seemed of sufficient value in the individual patient to press for its performance by an already over-burdened pathology service.

Gastroscopy. To be of value in deciding treatment gastroscopy must be done early, and it was performed in a proportion of cases in this series. Jones (1956) believed that gastroscopy is feasible and safe in such patients, but that it is best to wait until about six hours after a haemorrhage, to allow the stomach to empty. We concur with this view. That gastroscopy can be of great use in the diagnosis of the source of the gastroduodenal haemorrhage is exemplified by figures kindly provided by Dr. Avery Jones and Dr. Donald Kellock from the Central Middlesex Hospital, Park Royal (Table XV). During a four-year period gastroscopy was performed soon after admission in 190 cases of gastroduodenal haemorrhage. As a result a correct diagnosis was reached in 161 (85 per cent.). The examination was unsuccessful in 12 per cent., and in only 3·6 per cent. was a wrong diagnosis made. The combined use of oesophago-gastroscopy and barium-meal examination by Palmer (1957) resulted in a correct diagnosis of

the source of bleeding in 88·7 per cent. of 238 patients within a few hours of admission.

We are very appreciative of the help and co-operation of Mr. W. J. Ferguson and Mr. John Scholefield in the surgical treatment of these patients. We are especially indebted to Mr. Norman Tanner, Mr. A. M. Desmond, and Dr. B. F. A. Swynnerton for allowing us to quote the results in their cases at St. James' Hospital, Balham; and to Dr. F. Avery Jones and Dr. Donald Kellock for allowing us to quote their results of gastroscopy.

Summary

Prognostic factors in 325 cases of bleeding chronic gastric or duodenal ulcer have been assessed.

Patients with chronic gastric ulcers fared worse than those with duodenal ulcers. Male and older patients had a higher fatality rate. The prognosis was worse in patients with gastric ulcers who had melaena alone, and in all patients with a short ulcer history, or no history of previous bleeding. It was worse in patients who bled after admission to hospital, although emergency surgery greatly improved the outlook in such patients with gastric ulcers. Perforation was of very grave import. Associated diseases seemed to hasten death in a proportion of patients.

Venous congestion occurred in 13 per cent. of cases. It was no bar to surgery, provided it was of short duration. Adequate preliminary treatment with digoxin was considered to be important. Nevertheless, a raised venous pressure was a grave sign, especially in patients in whom the bleeding was not cut short by operation, and in patients whose blood-pressure fell. It may be an indication of underlying cardiac disability, and it is possible that early and adequate blood transfusion may prevent its onset.

Irrespective of age and sex, patients with bleeding chronic gastric ulcers responded better to emergency surgery (mortality 9 per cent.) than to medical treatment (mortality 23 per cent.). Patients with duodenal ulcers responded better to medical treatment (mortality 6 per cent.) than to emergency surgery (mortality 23 per cent.). Surgery may be an important means of reducing mortality in patients with bleeding chronic gastric ulcers, irrespective of age over 50 years or sex.

The results reported by Tanner, Desmond, and Swynnerton (1959) suggest that the routine use of emergency surgery for patients with bleeding chronic gastric and duodenal ulcers will not always improve the prognosis. The considerations we have brought forward, however, suggest that there are factors in the individual case of bleeding peptic ulcer which, if present, weight the scales in favour of emergency surgery. These are: (1) the presence of a large gastric ulcer as the source of bleeding; (2) a male patient over 50 years old; (3) a short ulcer history; (4) recurrent or continued bleeding after admission to hospital, especially from a chronic gastric ulcer, and especially if venous con-

gestion occurs; (5) the suspicion of perforation or carcinoma. If these criteria are valid, it is evident that it is important quickly to diagnose the site, size, and character of the ulcer. Early gastroscopy, possibly combined with other methods of investigation, will help to do this. All the other factors can be determined clinically.

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A CONTROLLED CLINICAL TRIAL OF LONG-TERM ANTICOAGULANT THERAPY IN CEREBROVASCULAR DISEASE[1]

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The assessment of any treatment of cerebrovascular disease is greatly handicapped by lack of knowledge of fundamental aspects of the condition. It is beyond the scope of the present paper to consider these difficulties at length, but the design and purpose of this clinical trial require that they be briefly summarized. The pathogenesis of cerebrovascular accidents is the subject of considerable disagreement among clinicians. Arterial spasm, thrombotic occlusion, embolic occlusion derived from atheromatous plaques in the great vessels of the neck, and insufficiency (the reduction of blood-flow through vessels narrowed, but not occluded, by atheroma), have all been advanced as possible causes of cerebral infarction. All these mechanisms may occur, but their relative frequency is unknown. Thus the clinician, faced with the individual patient, is unable with certainty to make a pathological diagnosis; indeed he has considerable difficulty even in making so gross a pathological distinction as between infarction and haemorrhage. The application of the criteria enumerated by Merritt and Aring (1937) on the basis of their clinico-pathological study, although of value, still leaves an uncomfortably large proportion of cases in which diagnostic certainty is lacking. Furthermore, the variation in the clinical pattern of the disease and the uncertainty of its natural history add difficulties to the appraisal of any form of treatment.

In addition to these factors relating to the disease itself, there are problems inherent in the application of the form of treatment under study which may complicate the assessment of its efficacy. In cerebrovascular disease the effect of anticoagulant therapy upon a recently established lesion is not entirely predictable. Thus it has been suggested (Brain, 1954; Symonds, 1956) that anaemic infarcts may become haemorrhagic under the influence of anticoagulants, and experimentally induced infarction in animals has been shown to behave in this way (Wood, Wakim, Sayre, Millikan, and Whisnant, 1958). On the other hand, Sibley, Morledge, and Lapham (1957) have failed to observe this effect in their experiments, nor can we be certain that experimentally induced

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infarction necessarily parallels naturally-occurring thrombotic occlusion. Apart from the particular case of cerebrovascular disease, the precise mode of action of anticoagulant drugs, and their influence on the course of occlusive vascular disease generally, are not fully understood, and consequently the definition of 'effective anticoagulation' is debatable. Furthermore, the treatment carries a risk of haemorrhagic complications; the frequency of these varies in different reported series, but their occurrence has always to be weighed against the possible benefit which the treatment may confer. The history of the use of anticoagulants in disease of the coronary arteries, which constitute a vascular system less complex than the cerebral arteries, bears out the reluctance of these drugs to yield to clinical appraisal.

In spite of all these foreseeable difficulties, there is a need in cerebrovascular disease for a trial of a form of therapy which theoretically might improve the outlook for the immense number of patients for whom, at present, we have so little to offer. In the presence of so many unpredictable factors the only satisfactory approach is by a strictly controlled clinical trial, in which the progress of patients receiving the treatment is compared with that of a similar group not so treated, but managed in the same way in all other respects over the same period of time. This we have endeavoured to do in our present study of the place of long-term anticoagulant therapy in the treatment of cerebrovascular disease.

Previous Studies

Apart from a single patient treated with heparin and described by Denber (1945), the first attempt to use anticoagulants as a long-term prophylactic measure in cerebrovascular disease was recorded by Rose (1950). Three patients suffering from hypertensive heart disease and 'spasm' of cerebral arteries were treated with dicoumarin. Since one patient had severe haematuria, and the other two had further minor disturbances of cerebral function within five and eight weeks respectively, the method of treatment was not considered to be of use, and was abandoned. Campbell (1953) described the beneficial effects of long-term anticoagulant therapy in a male patient aged 74 suffering from basilar artery thrombosis. Most previous studies have come from the United States, where comparisons of progress in patients during periods on and off treatment have been regarded as an acceptable method of control (Wright, 1957). Fisher and Cameron (1953) reported on a patient with basilar artery thrombosis whose fleeting attacks of ischaemia were absent for several months while on treatment with anticoagulants, and who relapsed on two occasions when they were withdrawn. At the first Princeton Conference on Cerebral Vascular Diseases, Fisher (1954) referred to 12 patients similarly treated, in whom results were promising, and the same author (1958) reported a series of 58 patients with symptoms and signs of the various stages of cerebral thrombosis due to atherosclerosis. Results suggested that 'anticoagulant therapy abolishes transient ischaemic attacks and prevents or postpones the arrival of a threatening stroke'. The group

included 22 patients with internal carotid–middle cerebral involve mentand 22 with vertebral-basilar disease; of the remainder, four had posterior cerebral and three lateral medullary syndromes, and in seven cases the anatomical diagnosis was uncertain. Benefit was measured by comparing the frequency of ischaemic manifestations during periods on and off treatment, but in addition comparison was made with 37 untreated patients, whose progress was found to be much less satisfactory than that of the treated group. In the latter group anticoagulant control was not uniform, and some patients also received hypotensive drugs. The author stated that the data did not provide incontrovertible evidence of the therapeutic efficacy of anticoagulants, because of the lack of satisfactory control patients.

Millikan, Siekert, and Shick (1955*a*) reported on the use of anticoagulant drugs in 26 patients suffering from basilar artery disease. Five showed features of intermittent insufficiency and, in all these patients, attacks ceased on therapy. The other 21 were thought to have thrombosis within the basilar arterial system, and three of them died in spite of treatment, whereas there were 10 deaths in a group of 23 untreated patients. The same authors (1955*b*) described the absence of ischaemic attacks in seven patients with intermittent insufficiency of the internal carotid arterial system treated by anticoagulants. In 1958 Millikan, Siekert, and Whisnant reported their experience in a much larger group of patients, totalling 317, all of whom received anticoagulants; 94 were classified as having intermittent insufficiency in the vertebral-basilar system, and 85 in the carotid system; 107 had irreversible vertebral-basilar thrombosis, and 31 had actively advancing carotid thrombosis. Treatment appeared to confer striking benefit in stopping ischaemic episodes in the 'insufficiency' groups and in reducing, in the 'thrombotic' groups, the mortality anticipated on the basis of the authors' observations of untreated patients. McDevitt, Carter, Gatje, Foley, and Wright (1958) summarized their 10-year experience in the use of anticoagulants in 100 cases of cerebral vascular disease; basing their observations on a comparison of periods on and off treatment, they concluded that anticoagulants substantially reduced the incidence of thrombo-embolic episodes; but, as 51 of their patients had rheumatic heart disease, and the authors did not differentiate in their analysis between embolism and thrombosis, their data cannot be interpreted in specific relation to the latter condition. It is considered that embolic infarction of cardiac origin is not strictly comparable for therapeutic purposes with thrombotic occlusion, because in the former case the cerebral vascular tree is not necessarily diseased. Schäfer (1959) also treated a group of 60 patients with cerebral thrombosis or embolism with anticoagulants but, comparing their progress with that of an untreated group, concluded that there was no significant difference.

There is thus a considerable weight of evidence to support the use of anticoagulants in chronic cerebrovascular disease, yet none of the studies referred to fulfil the criteria required in a strictly controlled trial. In particular, the use of the patient as his own 'control' is regarded as unsatisfactory in a disease in which we have so little knowledge of the natural history, and in which the course is so

variable and unpredictable (Marshall and Shaw, 1959). Furthermore, most authors have confined their attention to certain sharply defined diagnostic categories of cerebrovascular disease, though the issue that confronts the general physician, to whom the vast majority of patients with cerebrovascular disease is referred, is a broader one. In our experience the recognition of specific categories may be extremely difficult, and facilities for carotid and vertebral angiography are not everywhere available, even if such investigation were considered desirable. Patients of the type which is alleged to respond best to anticoagulant treatment are numerically few in proportion to the total number of cases of cerebrovascular disease, and reference to hospital at the stage of transient ischaemia, without established neural damage, is relatively uncommon. For these reasons we have based our study on a broader plan, by including a wide range of cerebrovascular cases commonly encountered in general medical practice. We have attempted to answer the questions as to whether or not long-term anticoagulant therapy (1) increases the expectation of life, or (2) decreases the incidence of further cerebrovascular accidents, or (3) influences the functional capacity of patients with cerebrovascular disease in general, or in specific sub-groups thereof. In the present paper only the first two considerations will be discussed.

Method

Patients were considered for inclusion in the trial who were under 70 years of age, and in whom there existed past or present evidence of neurological disturbance lasting for more than 24 hours, and judged by the clinician caring for the patient at the time, and by ourselves subsequently, to be attributable to non-haemorrhagic cerebral, carotid, or vertebral arterial disease. Admission was permissible at any time in relation to such disturbance, provided 14 days had elapsed since the last acute episode. Patients with a clinical diagnosis of cerebral aneurysm or angioma were excluded, as were patients suffering from intercurrent disease which presaged death within two years, or in which anticoagulant therapy was contra-indicated. Thus a history of peptic ulceration, haemorrhagic disease or recurring haemorrhage from any site, syphilis, malignant hypertension, and renal or hepatic disease, were regarded as grounds for exclusion. Patients who were pregnant, or in whom a need for intensive salicylate therapy was anticipated, were likewise not considered. Patients were also excluded if for personal, occupational, or geographical reasons it was thought that they would be unable or unwilling to co-operate sufficiently or to attend regularly for the necessary supervision. Candidates for the trial attended hospital on a day-patient basis for one day. The history was taken, and a full clinical examination made. The following investigations were carried out: X-rays of skull and chest, electrocardiography, blood-grouping and Wassermann reaction, blood urea and cholesterol, chemical and microscopic examination of the urine, and a water dilution test. Six records of resting blood-pressure were made at hourly intervals with the patient supine; levels of blood-pressure referred to subsequently are the mean of these readings.

To obtain uniformity in the application of the criteria of selection, the decision as to whether or not a patient was eligible for admission to the trial was taken by one of us (D. A. S.). The decision was made without knowledge of the treatment group to which the patient would be allocated. Patients admitted to the trial were differentiated by sex, and allotted by pairs to one of two groups by a randomization table. One group (high-dosage) received tablets containing 50 mg. phenindione ('dindevan'), the other group (low-dosage) received apparently identical tablets containing 1 mg. phenindione, an amount insufficient to interfere with the clotting mechanism. Patients did not know to which group they belonged, and were given the same advice regarding the possibility of haemorrhage and the action to be taken in the event of their requiring urgent medical or surgical treatment. Each was issued with a card stating his blood group and the address and telephone number of the hospital. It will be noted that no attempt was made to match the pairs in such features as age, blood-pressure, anatomical and pathological diagnosis, duration of symptoms, and frequency of ischaemic episodes. It was anticipated that with a large number of patients randomization would produce similarity in the two groups (*see p. 602*). The method does not, of course, preclude study of the data for defined sub-groups as well as for the total.

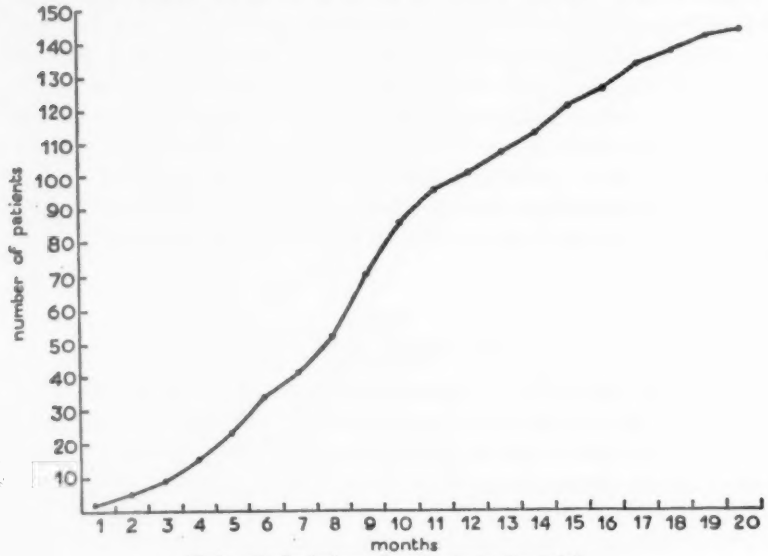
The Control of Therapy

All patients, in both high- and low-dosage groups, attended at one of four anticoagulant clinics, staffed by three doctors, at a frequency which varied between once weekly and once in four weeks, and at each attendance blood was taken for prothrombin estimation. The patients were seen regularly by the same doctor, but the dosage of tablets in both groups was controlled by one of us (D. A. S.), and was intimated to the patient, along with the time of the next visit, by postcard. The aim of treatment in the high-dosage group was to maintain the prothrombin time, estimated by the Quick one-stage method, at a level of two to two and a half times the control value. The prothrombin estimations were made by the same two technicians throughout the trial. When a further cerebrovascular accident occurred in a patient in the trial, treatment was continued with high- or low-dosage tablets according to the patient's group, unless there was indication of haemorrhage as shown by blood in the spinal fluid. In the latter case treatment was permanently stopped, as it was in the event of major extracerebral haemorrhagic complication, but the patient continued to be observed. In the case of minor haemorrhage the patient resumed therapy if it was deemed safe, provided the period of interruption of treatment had not exceeded 28 days. The same limit was set for patients whose therapy had to be interrupted for surgical treatment. If the period of interruption exceeded 28 days, treatment was not resumed, but the patient was followed up as usual. With regard to general measures, there was uniformity of management in the two treatment groups. Many of the criteria for selection and details of control and management, described above, were based on the plan of the Medical Research

Council (1959) trial of anticoagulant therapy in coronary thrombosis, to which access was kindly granted, and we gratefully acknowledge the help thus received.

Case Material

Between October 11, 1957, and June 5, 1959, 142 patients were admitted to the trial, 71 (47 men and 24 women) to the high-dosage group and 71 (47 men and 24 women) to the low-dosage group. The age distribution is given in Table I. The average age in the high-dosage group was 57·9 years (S.D. 6·9) and in the low-dosage group 58·2 years (S.D. 6·6). Table II gives the distribution of



Rate of admission of patients to the trial.

patients according to the anatomical site of lesion. When there was a history of more than one previous acute episode, the diagnosis was based on the most recent; Table III shows the frequency of previous attacks in the two groups. Table IV indicates the incidence of hypertension, patients being classified as hypertensive who had a mean diastolic pressure of 110 mm. Hg or above, on the basis of the average of the six resting readings taken before admission to the trial. The rate of admission to the trial was fairly uniform, as is shown in the Figure. The differences in the duration of treatment of patients in the two groups (Table V) are accounted for by the unequal distribution of deaths, haemorrhagic complications, and other causes of stoppage of treatment (Tables VII and VIII). The analysis of the case material has been given in these Tables and the Figure in some detail since, as mentioned earlier, a valid assessment of the results must depend upon the high- and low-dosage groups being homogeneous in respect of many variable features. Examination of the Tables shows that the randomization has, in fact, brought about two very similar and, therefore, comparable groups.

TABLE I

Age and Sex Distribution

Age (years)	*High-dosage group*				*Low-dosage group*			
	Male	*Female*	*Total*	*%*	*Male*	*Female*	*Total*	*%*
40–44	3	2	5	7.0	1	..	1	1·4
45–54	7	7	14	19·7	13	6	19	26·8
55–64	31	9	40	56·4	22	14	36	50·7
65–69	6	6	12	16·9	11	4	15	21·1
Total	47	24	71	100·0	47	24	71	100·0

TABLE II

Clinical Diagnosis

Site of lesion	*High-dosage group*				*Low-dosage group*			
	Male	*Female*	*Total*	*%*	*Male*	*Female*	*Total*	*%*
Hemisphere focal	29	19	48	67·6	33	16	49	69·0
Hemisphere diffuse	4	2	6	8·5	5	..	5	7·1
Brain stem	12	3	15	21·1	7	6	13	18·3
Internal carotid	2	..	2	2·8	2	2	4	5·6
Total	47	24	71	100·0	47	24	71	100·0

TABLE III

Frequency of Previous Attacks

Number of previous attacks	*High-dosage group*				*Low-dosage group*			
	Male	*Female*	*Total*	*%*	*Male*	*Female*	*Total*	*%*
1	34	18	52	73·2	33	22	55	77·5
2	9	5	14	19·7	8	2	10	14·1
3 or more	4	1	5	7·1	6	..	6	8·4
Total	47	24	71	100·0	47	24	71	100·0

TABLE IV

Incidence of Hypertension

Diastolic blood-pressure	*High-dosage group*				*Low-dosage group*			
	Male	*Female*	*Total*	*%*	*Male*	*Female*	*Total*	*%*
110 mm. Hg or above	13	11	24	33·8	14	10	24	33·8
Below 110 mm. Hg	34	13	47	66·2	33	14	47	66·2
Total	47	24	71	100·0	47	24	71	100·0

Results

The trial began on October 11, 1957, and was brought to an end in its present form on June 5, 1959. The results are summarized in Table VI. During the period of observation there were five non-fatal recurrences of cerebrovascular accidents in four patients in the high-dosage group, and four similar recurrences in three patients in the low-dosage group, a difference which is clearly not significant. On the other hand, in the high-dosage group there were four fatal

TABLE V

Duration of Treatment

	High-dosage group				*Low-dosage group*			
Months	*Male*	*Female*	*Total*	%	*Male*	*Female*	*Total*	%
0–	5	3	8	11·3	6	3	9	12·7
3–	10	5	15	21·1	7	4	11	15·5
6–	8	5	13	18·3	6	6	12	16·9
9–	13	7	20	28·2	14	6	20	28·2
12–	6	3	9	12·7	9	4	13	18·3
15–	3	1	4	5·6	2	1	3	4·2
18–20	2	0	2	2·8	3	0	3	4·2
Total	47	24	71	100·0	47	24	71	100·0

TABLE VI

Summary of Results

	High-dosage group			*Low-dosage group*		
Total number of patients	*Male* 47	*Female* 24	*Total* 71	*Male* 47	*Female* 24	*Total* 71
Non-fatal cerebrovascular accidents	3	2	5	4	..	4
Fatal cerebrovascular accidents	2	2	4	..	..	..
Deaths possibly attributable to treatment	1	..	1	..	..	..
Deaths from other causes	2	1	3	1	..	1
Progressive deterioration	..	1	1	1	..	1
Defaulters	..	..	..	1	1	2*

* One died of myocardial infarction, and one is alive and has had no further cerebrovascular accidents.

cerebrovascular accidents, and in the low-dosage there was none. Since all four deaths were due to cerebral haemorrhage, it must be questioned whether they have not arisen as complications of treatment rather than as incidents in the natural history of the disease. In addition there was one non-cerebrovascular death which must be similarly questioned, though the explanation of the cause of death in this patient (No. 8 in Table VII) was not entirely satisfactory. His condition on admission to hospital suggested a diagnosis of myocardial infarction, but at post-mortem examination this was not confirmed. Nevertheless, a moderate amount of blood, which was not measured, was found in the pericardial

sac, and although there was no other evidence of spontaneous haemorrhage, and the prothrombin time was within the therapeutic range, it was felt that the death must be added to those possibly attributable to treatment. The probability of observing by chance five deaths in the one group and none in the other is 0·058 (exact test) or odds of about 17 to 1. In other words it does not quite meet the customary 20 to 1 significance level.

TABLE VII

Causes of Death

	Case number	*Age (years)*	*Sex*	*Blood-pressure*	*Prothrombin time**	*Diagnostic group*	*Duration of treatment*	*Cause of death*
High-dosage group	8	58	M	180/100	×2·2	Hemisphere diffuse	11 months	Haemopericardium†
	30	57	M	170/114	×1·8	Hemisphere focal	3 months	Cerebral haemorrhage†
	43	69	F	200/134	×3·1	Hemisphere focal	11 months	Cerebral haemorrhage†
	46	68	M	155/100	×2·3	Hemisphere focal	4 months	Cerebral haemorrhage†
	78	62	M	168/100	×2	Hemisphere focal	5 months	Myocardial infarct†
	91	46	F	220/120	×3	Brain-stem	6 months	Congestive heart failure†
	134	56	F	230/122	×2·4	Brain-stem	2 months	Cerebral haemorrhage†
	137	63	M	144/84	×4	Hemisphere focal	2 weeks	Carbon monoxide poisoning† (suicidal)
Low-dosage group	65	68	M	156/100	×1	Hemisphere focal	7 months	Myocardial infarct
	4‡	67	M	150/95	×1	Hemisphere focal	1 month	Myocardial infarct

* Last recorded reading expressed as multiplication factor of control time.
† Confirmed by autopsy.
‡ Patient defaulted and subsequently died.

TABLE VIII

Complications of Treatment

	High-dosage group			*Low-dosage group*		
	Male	*Female*	*Total*	*Male*	*Female*	*Total*
Total number of patients	*47*	*27*	*71*	*47*	*24*	*71*
Haemorrhage; treatment interrupted	5	8	13	1	..	1
Haemorrhage; treatment abandoned	2	..	2	..	..	..
Hypersensitivity; treatment abandoned	..	1	1	..	..	..
Intercurrent illness; treatment abandoned	..	..	..	..	1	1

The causes of death are listed in Table VII. Five of them, Nos. 4, 65, 78, 91, and 137, are regarded as not directly related to the primary disease or to treatment and, of these deaths, three occurred in the high-dosage group and two in the low-dosage (including the defaulter), an insignificant difference. In only one of the four patients who died from cerebral haemorrhage (No 43) was the last recorded prothrombin time outside the therapeutic range, but, at 3·1 times the control, it was not excessive. Three of these four patients had diastolic blood-pressures above 110 mm. Hg, and in two of them post-mortem examination suggested that the original lesion had been due to haemorrhage and not to

thrombosis. Reviewing their case histories, it was not possible to discern any clinical features which might have indicated a diagnosis of haemorrhage rather than thrombosis, yet in retrospect it seems probable that they were admitted to the trial on the basis of an erroneous diagnosis.

The patients who defaulted, and those in whom treatment had to be abandoned owing to progressive deterioration in their general condition, have all been traced. One (included in the comparisons of deaths) had died from myocardial infarction, but none had sustained a further cerebrovascular accident, so that they do not influence the analysis. Haemorrhagic complications were not excessive as compared with other series, but in two instances treatment had to be abandoned (Table VIII).

Discussion

The trial was stopped in its present form earlier than had been anticipated, because of the emergence of a disturbing picture. Non-fatal cerebrovascular accidents were distributed about equally to the two groups (5 to 4), and so were deaths due to unrelated causes (3 to 2). On the other hand, the haemorrhagic fatalities that might be due to the treatment were very unevenly divided (5 to 0). While this difference does not quite reach the 0·05 level of significance, it so closely approaches it as to pose a serious ethical problem.[2] It may well be that long-term anticoagulant therapy in patients with cerebrovascular disease carries a significant hazard of cerebral haemorrhage. Previous workers with anticoagulants in this field have not been unaware of such occurrences. McDevitt, Carter, Gatje, Foley, and Wright (1958) encountered five instances of cerebral haemorrhage, three of which were fatal, and two instances of subarachnoid haemorrhage. Fisher (1958) mentioned two fatal cases of cerebral haemorrhage, but they were not included in his series of 58 patients. Schäfer (1959), whose 60 patients were treated for only a short period, also had three fatal cases of cerebral haemorrhage. Our figures are thus comparable, but are thrown into bolder relief by comparison with the low-dosage group, emphasizing that without a controlled trial the implications of such an incidence are liable to be overlooked.

There are several possible explanations as to why patients with cerebrovascular disease on anticoagulant therapy should be prone to cerebral haemorrhage. Firstly, it might be argued that they were instances of thrombotic infarction in which bleeding was induced; but one would then expect to have encountered a comparable group of thromboses in the low-dosage group. Secondly, it may be that anticoagulant therapy *per se* tends to cause cerebral haemorrhage; yet only one case of cerebral haemorrhage occurred in the large series of patients with coronary artery disease so treated in the Medical Research Council's (1959) trial. Thirdly, it could be argued that the deaths in our series were attributable to inadequate control of therapy; that an 'effective' therapeutic range was achieved is borne out by the fact that a difference between the two groups

[2] If it be believed that to such a group of patients the anticoagulant treatment could bring no benefit but could conceivably do harm, then the adverse difference in mortality between the treated and control groups would certainly be significant (P approximately 0·03 in the appropriate one-tail test).

emerged, but the comparatively low incidence of extracerebral haemorrhagic complications confirms the view that the high-dosage group were not over-treated. A fourth, and in our view the most likely explanation, is that small contained haemorrhages are a commoner cause of transient cerebrovascular accidents than has formerly been supposed, such lesions being indistinguishable by present methods from non-haemorrhagic infarcts. It would appear that recurrences of the latter have been evenly distributed to the two groups, but that there is an increased liability for haemorrhagic lesions to recur in the presence of anticoagulant therapy, and for these to be devastating in their effects. A cerebral haemorrhage, once started, is unlikely to be self-limiting in a patient receiving anticoagulant therapy, so that one would not expect a corresponding increase in non-fatal recurrences. A striking example was seen in Case 43 (Table VII). In May 1958 the patient suddenly developed dysphasia and weakness of the right upper limb, with no headache, vomiting, or loss of consciousness. She was admitted to another hospital, where she was found to have dysphasia and a right hemiparesis, and recovered within 48 hours. A month later, when she was admitted to the trial, there were no residual signs. Eleven months later she suddenly lost consciousness, and died within 24 hours. Autopsy (Professor W. Blackwood) showed the cause of death to be a massive cerebral haemorrhage in the right hemisphere. In the left hemisphere, however, there was the residuum of an old small haemorrhage. It seems clear that this was the cause of her transient symptoms in May 1958.

Of the four fatal cases of cerebral haemorrhage, three came from the 24 patients who were hypertensive by our definition, and one from the 47 who were not hypertensive; the difference is not statistically significant. Carter (1957) and others, however, have suggested that anticoagulants carry a higher risk of haemorrhagic complications in elderly and in hypertensive patients; yet in the Medical Research Council's trial (1959) only those hypertensive patients who were in the malignant phase were excluded, and the incidence of complications was not high. In view of the present results, however, it was decided to bring the present trial to an end, and to restrict the further use of anticoagulants to diagnostic groups for which particular claims of efficacy have been made.

On the basis of some of the results already reported from the United States, when this trial was set up it might perhaps have been argued that it was unethical to withhold the treatment from half the patients. The wheel has turned so far that we feel it is unethical to proceed with the treated group without making the modification described. Although this result has emerged from the mortality figures, no conclusion can be drawn from the comparison of the non-fatal recurrence rates in the two groups. The low incidence of further non-fatal cerebrovascular accidents in the high-dosage group regarded in isolation might well give rise to the clinical impression that treatment had been beneficial. Yet comparison of the results with those in the low-dosage group clearly shows that this is not so. Indeed, the recurrence rate in the latter group is so low over the period of follow-up that any form of treatment would require to be almost one hundred per cent. effective, and devoid of serious hazard, before it could claim

to be of definite value. A longer period of follow-up, however, will be required before this point can be settled.

In conclusion, the present study strongly indicates that the general use of anticoagulant therapy in patients with cerebrovascular disease, who are selected and managed along the lines adopted in this trial, is hazardous, because of the risk of cerebral haemorrhage. This risk is present even when the anticoagulant therapy is carefully controlled, and the prothrombin time maintained at a level which is generally accepted to be safe. It may be that certain restricted types of cerebrovascular disease gain benefit from anticoagulant therapy, but, in view of the many variable factors present in the condition, this can be ascertained only by properly designed and strictly controlled clinical trials.

We wish to thank most sincerely the many people who helped us with this trial: the physicians and surgeons who referred patients, and particularly Dr. R. P. K. Coe, Dr. Q. J. G. Hobson, and Dr. E. C. O. Jewesbury, and the medical committees of the West Middlesex and North Middlesex Hospitals where anticoagulant clinics were held. We are indebted to Professor J. N. Cumings and Dr. W. H. McMenemey, in whose laboratories the prothrombin estimations were made, and to Mr. B. Skinner, Chief Pharmacist at the National Hospitals. Evans Medical Supplies Limited kindly supplied low-dosage tablets and medical cards for patients to carry. Finally, we are most grateful to the Nuffield Foundation for their generous support of this investigation at all its stages.

The Hospital Case Numbers of the patients referred to were as follows: No. 8, 39985; No. 30, 77964; No. 43, 79129; No. 46, 79520; No. 78, 69655; No. 91, 20508; No. 134, 85107; No. 137, 85882; No. 65, 80100; No. 4, 39732.

Summary

A controlled clinical trial of long-term anticoagulant therapy in chronic cerebrovascular disease has been described. One hundred and forty-two patients were included in the study, and were divided by random allocation into two groups; one of these, the high-dosage group, was treated with phenindione, the prothrombin time being maintained at two to two and a half times the control. The other, the low-dosage group, received identical tablets containing a quantity of phenindione insufficient to alter the clotting mechanism, but in all other respects was managed in the same way as the high-dosage group.

The incidence of further non-fatal cerebrovascular accidents did not differ significantly between the two groups, but there were four deaths from cerebral haemorrhage and one from haemopericardium in the high-dosage group, compared with none in the low-dosage group. (The difference is not quite formally significant.) It has been concluded that, although anticoagulant therapy may be of benefit in certain restricted types of cerebrovascular disease, its general use in cerebrovascular disease may carry a definite hazard of cerebral haemorrhage.

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INGRAVESCENT CEREBRAL INFARCTION[1]

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(From Ashford Hospital, Middlesex)

The treatment of cerebral infarction still remains a considerable problem, particularly with regard to the use of anticoagulant therapy. Previous reports (Carter, 1957, 1959) have suggested that cerebral embolism and non-embolic cerebral infarction of slow onset are the most promising conditions for this treatment, and in view of the continuing uncertainty it was decided to review patients with cerebral infarction of slow onset in order to discover whether their natural history would be improved.

Patients Investigated

The present review includes all patients below the age of 80 with a history of cerebral infarction taking more than two hours to reach its maximum effect. The patients were consecutively admitted to the Ashford Hospital, Middlesex, from the beginning of 1955 to the end of 1958, and were all seen and treated personally through the generosity of my colleagues. Alternate patients were treated with anticoagulants, and the results with regard to survival and degree of recovery were compared with those obtaining in the remaining, untreated, group. For this purpose a final assessment was made at the end of six months, this investigation being concerned with the immediate results. During this four-year period 298 patients below the age of 80 were admitted suffering from cerebral infarction; 36 were diagnosed as having cerebral embolism, and the remaining 262 as having non-embolic cerebral infarction (cerebral thrombosis). In 90 of the latter patients a history of increasing disability was obtained, or a progressive neurological deficit was observed, of more than two hours' duration. Forty-five of these 90 patients were treated with anticoagulants, leaving a numerically equal comparable group.

The total figures have been analysed in Table I, and here it must be remembered that among the 57 per cent. suffering from 'sudden' non-embolic infarction were patients who woke to find themselves paralysed, or who were found unconscious. These numbered 80 in all, representing 27 per cent. of the total admissions, and it is probable that among them were patients in whom the onset might have been measured in hours, had they been able to remember. Therefore this series of patients with ingravescent infarction cannot include all those with slow-onset stroke; but this defect will obviously apply equally to all reports. Fig. 1 shows the relationship between age and sex, and in view of

[1] Received October 21, 1959.

the equality in numbers the inequality of age distribution is of interest. Only in the age group 70 to 79, by far the largest, do women outnumber men; although this may be due to more women surviving, it may be associated with their oestrogenic protection from atheroma up to the menopause, with a consequent delay in the onset of cerebral atheroma as compared with men. These

TABLE I

Patients with Cerebral Infarction Admitted to Ashford Hospital, showing Type of Infarction

Year	*Number of patients*	*Embolism*	*Rapid-onset infarction (under 2 hours)*	*Slow-onset infarction (2 hours and over)*
1955	70	9	37	24
1956	72	9	39	24
1957	76	10	46	20
1958	80	8	50	22
Total	298	36	172	90
Per cent.	100	12	58	30

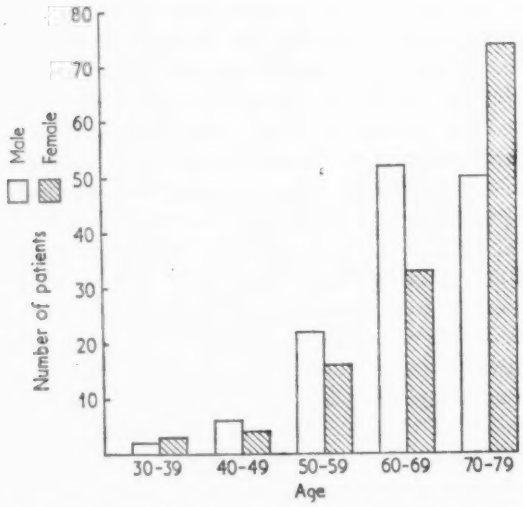

FIG. 1. Relationship between age and sex in cerebral infarction.

figures are in accord with Glynn's (1956) series; but American figures (Fisher, 1958; Merritt, 1954; Murphy, 1954) suggest that cerebral infarction is much commoner in men than in women, and here the selection of patients below the age of 70 could well account for the discrepancy. Comparison of the treated and control groups shows that both are reasonably similar with regard to age and sex distribution (Table II).

Diagnosis

The diagnosis of cerebral infarction was made on the appearance of a persisting focal neurological disorder in the distribution of one of the major cerebral arteries, with or without unconsciousness, without any evidence of embolic source, without any history of preceding head injury, and with the cerebrospinal fluid normal to the naked eye. In addition, it was noted that any worsening of the clinical condition almost always occurred in an irregular or stepwise way, with either sudden deepening of the degree of weakness in

TABLE II

Age and Sex Distribution of Both Series

	Treated patients				*Untreated patients*			
	Male		*Female*		*Male*		*Female*	
Age (years)	*Number*	%	*Number*	%	*Number*	%	*Number*	%
40–49	2	8	1	5	0	0	2	9
50–59	7	28	4	20	7	30	3	14
60–69	10	40	6	30	11	48	7	32
70–79	6	24	9	45	5	22	10	45
Total	25	100	20	100	23	100	22	100

any one part, or spread of the weakness to previously unaffected areas. The subsequent course was either a general worsening of the patient's condition, and death within a few days or weeks, or gradual improvement within three or four days, with recovery of function to a variable degree. In this stage of recovery a similar but less obvious stepwise character was seen, the patient suddenly noticing, to his surprise, movement at a joint previously immobile. To the above positive definition it is necessary to add that there should be no clinical evidence of tumour, abscess, or subdural haematoma. In this series the greatest trouble arose with differentiation of infarction from an intracranial haematoma, and from tumour with adjacent thrombosis. Admittedly the cases of haematoma showed a smoother course in loss of neurological function, and more fluctuation in the patient's awareness of his surroundings; and in most cases adjacent parts of the brain were directly involved, so that a classical cerebral artery syndrome was not seen. Reliance on a clear cerebrospinal fluid, together with the above criteria, seemed to produce the best diagnostic results, but the following case histories illustrate the difficulties and the mistakes.

A man of 60 (Case 23, 1955) gave a history of a number of 'little strokes' for three or four days before a severe left hemiplegia occurred, and was said to have had attacks of 'painful clumsiness' of the left hand during the previous six months. He died while receiving full anticoagulant therapy; at autopsy there was surprisingly little atheroma of the cerebral vessels, and no occlusion or stenosis of the carotid or vertebral-basilar system, but a recent clot was present in the right middle cerebral artery, and was beginning to organize. A cavity was found involving the lentiform nucleus, the internal capsule, and the outer half of the thalamus, and no haemorrhages were found in the brain.

Histology showed this cavity to be in an astrocytoma, and it was obvious from the age of the clot that it had started near or in the tumour and spread proximally along the middle cerebral artery.

A woman aged 64 (Case 40, 1958) was admitted with the history that four days previously she had found her left arm weak, and the next day the left side of her face had dropped. Some improvement occurred until the day before admission, when on getting out of bed she fell owing to unsuspected weakness of her left leg. There was no other history of injury. On admission she was mentally alert, and had a moderately severe left hemiparesis, with left extensor plantar response; the weakness seemed to involve the arm, leg, and face equally. There was slight loss of tactile discrimination in the left hand, and some loss of position sense, with hypalgesia, in the left foot; there was no visual-field defect. The cerebrospinal fluid was clear and under normal pressure; it contained 20 red cells per cu. mm., and 45 mg. of protein per 100 ml. Pulsation in the neck was normal, and a diagnosis of right middle cerebral occlusion was made, although it was noted that the uniformity of the left-sided weakness was a little unusual in patients without complete hemiplegia suffering from cerebral infarction. Anticoagulant therapy was begun, but was discontinued after 24 hours because the patient became suddenly worse, with restless stupor, left-sided involuntary movements, and bilateral extensor plantar responses. The fundi remained normal, but both pupils became enlarged, with a sluggish response to light, and the pulse slow. A right carotid arteriogram showed the presence of a left fronto-parietal subdural haematoma, and no evidence of arterial occlusion. Operation confirmed the diagnosis, and recovery ensued without permanent disability.

This case was a little difficult, for it is possible that the original diagnosis of cerebral infarction was correct, and that the patient's fall on the day before admission produced the acute subdural haematoma. It is also possible, however, that the whole picture was due to the haematoma, and it is disconcerting to think that anticoagulants were used for this condition. This difficulty in diagnosis has been emphasized by Kelly (1958), and more recently McKissock, Richardson, and Walsh (1959) have shown that about 10 per cent. of their proven cases of intracerebral haematomata occurred in normotensive patients, and showed a slow onset without loss of consciousness and with clear cerebrospinal fluid. These authors, however, did not mention any stepwise character in the development of the lesion in their patients, and this feature, together with limitation of the lesion to the territory of one cerebral artery, may be helpful in diagnosis.

Whenever there was doubt about the diagnosis, or when the subsequent course suggested that the original clinical impression of infarction was wrong, recourse was had to cerebral angiography. This investigation was made in 15 patients admitted with the diagnosis of cerebral thrombosis of slow onset, in whom the clinical examination in hospital suggested some other cause for the lesion. Six were clinically diagnosed as having cerebral haematomata, and nine as having atypical cerebral infarction, or possibly tumour. Four of the former group were confirmed as having haematomata (in three cases intracerebral, and in one subdural) and two showed cerebral vascular occlusion. Of the group thought to have atypical infarction or tumour, three were confirmed

as suffering from cerebral vascular occlusion, two were shown to have a subdural haematoma, two a large glioma, one an intracerebral haematoma, and one a normal arteriogram.

In one case an incomplete hemiparesis became complete after carotid arteriography, which showed carotid stenosis, and in one other the hemiparesis became worse, but after two days returned to its previous extent. The diagnosis in this patient was confirmed as occlusion of the middle cerebral artery; in no case was vertebral angiography thought to be justified, owing to its dangers in patients suffering from cerebral atherosclerosis.

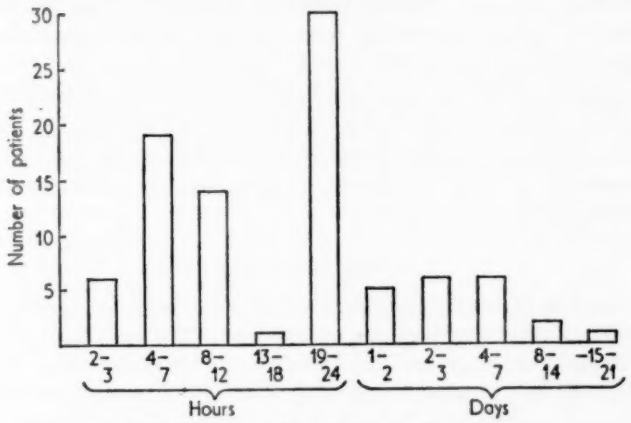

FIG. 2. Time of evolution of strokes.

The term 'ingravescent' must now be defined. It is here used to describe cerebral infarction of gradual onset in which the neurological deficit is still incomplete after two hours or more. This arbitrary period is used because most cases fall well to one or other side of this line. For this type of stroke many terms are in current use: 'slow-onset stroke', 'ingravescent stroke', 'progressive infarction', and 'stroke in evolution' (Fisher, 1958). Much confusion has been caused by the word 'stroke', which is used sometimes for the first symptom or sign of brain damage, sometimes for the neurological deficit, and sometimes for the state of consciousness or otherwise. Moreover, it may include all types of lesion, from a hypertensive cerebral crisis, through embolism and thrombosis, to any sort of intracranial haemorrhage. It would probably be as well, therefore, to avoid this word in medical terminology, in the same way as the phrase 'heart attack' is no longer used, although some may feel that it remains a useful short description for any type of acute cerebrovascular lesion. In the present series it was found that the duration of the development of the neurological lesion varied from two hours to three weeks, but only a few patients were found at these extremes, as is shown in Fig. 2.

Distribution of Infarction

By far the commonest type of infarction was in the internal carotid–middle

cerebral territory. Out of the total of 262 non-embolic infarctions, 225 were in this group, 25 were in the vertebral-basilar territory, seven were occlusions of the posterior inferior cerebellar artery, three were posterior cerebral, and two were anterior cerebral. This proportion of nine middle cerebral to one basilar infarction agrees with the findings of Hutchinson and Yates (1957), who found occlusion of the hind-brain arteries within the skull in only three of 35 patients who had died of 'cerebral thrombosis'. They pointed out, however, that stenosis or occlusion of the cervical portion of one vertebral artery probably played a part in the final infarction of brain tissue in 12 patients. American figures are very different: Adams (1958), for example, over a five-year period, investigated 58 patients suffering from cerebral thrombosis, and found the distribution to be internal carotid–middle cerebral in 22, vertebral-basilar in 22, posterior cerebral in four, a lateral medullary syndrome in three, and uncertain in seven. This surely must have been a very selected group. The figures given by Murphy (1954) are nearer those of the present series, showing a middle cerebral territory in 65 to 75 per cent. of cases, posterior cerebral 10 to 15 per cent., and basilar in 10 per cent.

Method of Treatment

In the treated group anticoagulant drugs were used in the following way. Once the diagnosis of ingravescent cerebral infarction had been made, 12,500 units of heparin were given intravenously, followed by two similar doses intramuscularly at six-hourly intervals. With the first dose of heparin, oral phenylindanedione was begun, so that a continuous anticoagulant effect was maintained from the beginning. At first the dosage of phenylindanedione was 300 mg. in divided doses for the first 24 hours, 200 mg. for the next 24 hours, and then usually from 50 to 100 mg. daily according to the prothrombin time. It was soon found that in some patients this dosage produced prothrombin times greater than desired, and the subsequent practice has been to give 200 mg. for the first 24 hours, 150 mg. for the next 24 hours, and thereafter doses sufficient to keep the prothrombin time between two and three times the normal length of approximately 12 seconds. As these patients were in hopsital, prothrombin times were estimated daily. Prothrombin percentages were also recorded, but were not considered to have any advantage over the prothrombin time. Treatment was continued for three weeks at full dosage, and then tailed off for the fourth week. In previous years two weeks' treatment was considered adequate, since it has been shown to be so in thrombo-embolism of the limb vessels, both arterial and venous. Occasional relapses, however, occurred in the third week, suggesting that this period was not long enough; therefore a full three-week course was given to every treated patient, followed by a slow reduction for the fourth week, so that the prothrombin time did not fall to normal too quickly.

The dangers of anticoagulant treatment have been emphasized and reviewed by many authorities (Adams and van der Eecken, 1953; Sibley, Morledge, and Lapham, 1957; Moyes, Millikan, Wakim, Sayre, and Whisnant, 1957; Elkington,

1955). In the present series 17 minor haemorrhagic episodes occurred in nine patients: haematuria accounted for seven, epistaxis for five, subconjunctival haemorrhage for three, and facial bleeding after shaving for the remaining two. In only one of these cases was the prothrombin time found to be over 40 seconds, and in none was the treatment discontinued because of the bleeding. No major visceral bleeding was encountered, and no patient had to be withdrawn from the treated group. In only one patient subjected to autopsy was there a suggestion that anticoagulants had contributed to death. The history of this important case is given in detail.

J. S., a man aged 67 (No. 26190), was admitted in November 1958 with a history of progressive vertigo, homonymous hemianopia, and progressive weakness of the legs. He had noticed difficulty in seeing objects to the left, and an increasing tendency to fall backwards, and for three weeks before admission had found that his legs were too weak to support him. There was some difficulty in initiating micturition, but no incontinence. On the day of admission he was found lying in a dazed and stuporose condition on his kitchen floor.

On admission he was conscious but confused, with a left hemiparesis and left hemianopia. No sensory loss could be detected, but his answers seemed unreliable. His family said that a year previously he had lost the use of the right side of the body for a few days, and that since then he had been giddy, unreliable in his habits, and refusing to shave or to go out of doors. He was occasionally noisy at night, and difficult to handle. Lumbar puncture showed clear cerebrospinal fluid under normal pressure, with 9 lymphocytes per cu. mm. and 50 mg. of protein per 100 ml., and the skull was radiologically normal. The blood-pressure was 135/85. Apart from a fixed and irregular left pupil, said to be due to injury 40 years previously, and some bilateral facial weakness, the cranial nerves appeared normal. The next day the left hemiparesis had increased in depth, and anticoagulant treatment was begun; the provisional diagnosis was basilar stenosis with possible thrombosis. The patient improved, and was walking about the ward within two weeks, but the hemianopia remained nearly complete, although central vision was spared. After his discharge treatment with anticoagulants (phenylindanedione 50 mg. daily) was continued, and the prothrombin time was constant at about 28 to 32 seconds.

Six weeks after discharge he complained of violent pain in his head and neck, and became rapidly unconscious. On readmission he was deeply comatose, and all the limbs were flaccid, but his neck was stiff. He died almost immediately, and the prothrombin time was 20 seconds. At autopsy a massive subarachnoid haemorrhage was found and, in spite of the relatively short prothrombin time, it was thought that anticoagulants might have contributed to death. The main haemorrhage, however, was found at the right border of the circle of Willis, adjacent to a friable tumour which was adherent to the wing of the sphenoid, and this tumour had ruptured the cavernous sinus. Sections showed that the tumour was a cellular meningioma. The vessels of the brain were grossly atheromatous, with stenosis most marked in the basilar artery about 1 cm. rostral to its origin from the vertebrals. The cervical carotid and vertebral arteries were atheromatous, but patent. No thrombosis was found, and the right posterior cerebral artery was narrower than the left, but not occluded, although the right occipital lobe was smaller than the left and showed recent softening.

This patient had a proved basilar stenosis, no evidence of clotting in the

atheromatous basal cerebral vessels, infarction of the right occipital lobe, and an unsuspected sphenoidal meningioma. The immediate fears that a controlled anticoagulant régime had killed him were allayed by the autopsy findings.

Results

Assessment. All the patients were followed up for six months, the investigation being concerned with survival and with the degree of recovery where this occurred. The final assessment of the degree of recovery was made quite simply on the patient's ability to get about and enjoy the usual amenities of life. Surviving patients were divided into five grades:

Grade I: no disability.
Grade II: slight disability, not interfering with the patient's way of life.
Grade III: disability requiring slight assistance from others.
Grade IV: disability requiring considerable assistance from others.
Grade V: patient bedridden.

This grading is a very slight modification of that suggested to me by Dr. John Marshall, and approximates to the usage of cardiologists in assessing the results of cardiac infarction. It has the additional advantage of arranging itself into two main types of grading, as Grades I, II, and III together can be considered good results, and compared with the bad results in Grades IV and V and with the deaths.

Analysis. In the first place, analysis of the untreated group shows the natural history of ingravescent infarction, and can be compared with the outcome of cerebral infarction as a whole and with other reports. These results are shown in Figs. 3 and 4, where it appears that of the 45 control patients 20 (44 per cent.) were in the 'good results' class, and 25 (56 per cent.) either unimproved or dead, after six months. In the case of all patients with cerebral infarction who received no specific treatment, the results were good in 37 per cent. and bad in 63 per cent. This suggests a slight but not significant improvement in the prognosis of ingravescent infarction as compared with other types, and the difference is enhanced by comparing the results with those found in the 172 patients who had sudden or overnight infarction, of whom 51 (30 per cent.) showed a good result and 121 (70 per cent.) a bad result. Glynn's figures (1956) provide an interesting comparison. He studied the results in 315 patients admitted to St. Mary Abbot's Hospital, London, in the years 1951 to 1954 inclusive. One hundred and sixty-four were diagnosed as having thrombosis; in 71 per cent. of these the onset was sudden, or the patient woke to find the stroke fully developed, in 20 per cent. it was gradual, and in nine per cent. unknown. Glynn found no difference in the prognosis between these groups, and his final figures showed that 37 per cent. of the patients died, 17 per cent. had little or no recovery of function, 39 per cent. could walk with the help of a stick, and 7 per cent. had no real disability. Divided into the broad 'good' and 'bad' results, his figures are 46 per cent. good and 54 per cent. bad, compared with the present series, which shows 37 per cent. good and 63 per cent.

bad. In another report (Carter, 1959) the results for slow-onset stroke not treated by anticoagulants are 52 per cent. good and 48 per cent. bad, compared with 48 per cent. good and 52 per cent. bad for all infarctions.

From all these figures the natural history of cerebral infarction seems clear,

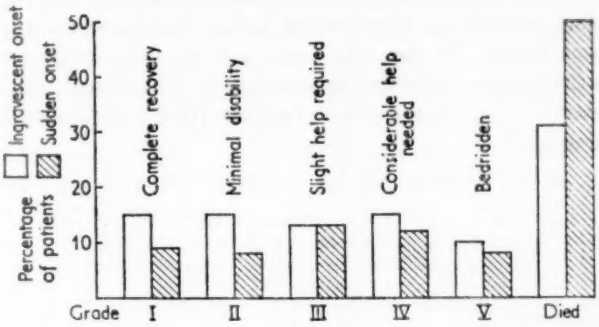

FIG. 3. Percentage results in untreated cerebral infarction.

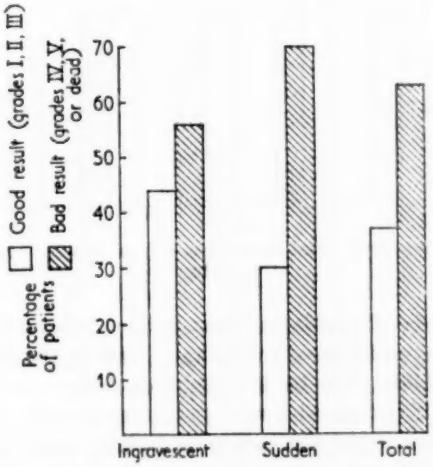

FIG. 4. Relation of prognosis to onset in untreated patients.

just under half the patients making a fair or good recovery, and over half dying or being left with a considerable disability. In sudden-onset infarction the figures are a little worse, twice as many patients doing badly as those doing well, and half the patients dying within six months.

In the treated series, comprising 45 patients with slow-onset infarction who received anticoagulant therapy for four weeks, the results show that 25 were in the 'good result' groups and 20 in the 'bad', and the details are shown in Fig. 5. These figures compare favourably with the results in the untreated series of patients with slow-onset infarction, of whom 20 were in the 'good

result' groups and 25 in the 'bad'; but, although the trend toward recovery is improved, the difference is only just significant.

Further analysis seemed desirable along two possible lines. The first was the possibility that the prognosis might vary with the length of time the disability had been present before treatment, and the second was the separation from the other patients of those whose stroke had become complete before treatment was begun. In the first case no prognostic significance could be attached to the length of interval between onset of the stroke and commencement of treatment; but in the second case the results of further studies were more encouraging.

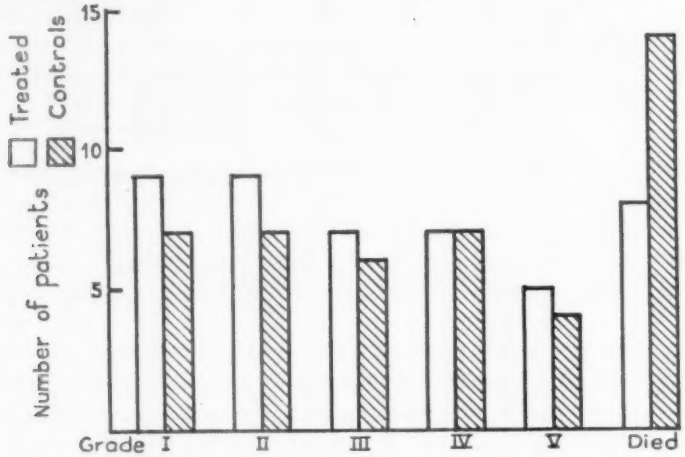

FIG. 5. The results in treated patients compared with controls at six months.

Of the treated series, 25 patients began anticoagulant treatment before the stroke was complete, and after six months 17 were in the 'good result' group, six having no disability, five having slight disability, and six needing only slight assistance. Of the 20 who were not treated until the hemiplegia had reached its maximum, eight patients were in the 'good result' group. This means that 58 per cent. of the patients treated before the stroke was complete did well, compared with 40 per cent. of those treated later. This is a significant difference, both in comparison with the general prognosis of all types of cerebral infarction and in comparison with the prognosis of slow-onset stroke. It might be argued, however, that simple admission to hospital, without specific treatment, before the climax of a stroke, carries a better prognosis than admission after the stroke is complete. The control series was therefore similarly studied, to determine whether patients admitted before the stroke was complete did better than those admitted afterwards, and the results of this comparison in both series are shown in Table III. This shows a significant improvement in the prognosis of patients who were treated with anticoagulants while their infarction was still in the ingravescent stage ($P < 0{\cdot}05$). In the control series

23 patients were admitted with the stroke incomplete, and 22 with it complete. Of the former, 11 made a good recovery, six made little or no recovery, and six died; of the latter, nine made a good recovery, five little or none, and eight died. Although figures for the incomplete stroke are a little better, they are not significantly so, 48 per cent. of the patients with an incomplete stroke having recovered, compared with 41 per cent. of those in whom it was complete. In the treated series 25 patients were admitted with the stroke incomplete, and 20 with it complete. Of the former, 17 made a good recovery, seven little or none, and one died; of the latter, eight made a good recovery, five little or none, and seven died. Thus 68 per cent. of the treated patients with incomplete strokes recovered, compared with 40 per cent. of those with complete strokes. These figures can be compared with those shown in the untreated series (recovery in 48 per cent. of the incomplete strokes and in 41 per cent. of the complete strokes). In spite of the small numbers, this 68 per cent. recovery is significantly higher than the percentage of recovery in the other three groups, and suggests that the ideal patient for this form of treatment is one suffering from an incomplete ingravescent cerebral infarction.

TABLE III

Relationship of Recovery to Degree of Stroke on Admission or Treatment

	Treated patients		*Untreated patients*	
	Anticoagulants before stroke complete	*Anticoagulants after stroke complete*	*Admitted before stroke complete*	*Admitted after stroke complete*
Grade I: no disability	6	3	4	3
Grade II: slight disability	5	4	4	3
Grade III: needing slight assistance	6	1	3	3
Grade IV: needing considerable help	4	3	3	4
Grade V: bedridden	3	2	3	1
Dead	1	7	6	8
Total	25	20	23	22
Percentage of good results (Grades I, II, III)	68	40	48	41
Percentage of bad results (Grades IV, V, and deaths)	32	60	52	59

Discussion

Previous experience (Carter, 1957, 1959) has suggested that vasodilator drugs and stellate-ganglion block have no place in the treatment of cerebral thromboembolism, and that anticoagulant therapy has improved the prognosis of cerebral embolism and possibly helped the patient with slow-onset cerebral infarction. Current reports still show some disparity in results of treatment, and reflect a persisting conflict of medical opinion concerning the use of

anticoagulant drugs in cerebral vascular disease. Millikan, Siekert, and Whisnant (1959) suggested four indications for this type of treatment. These are:

1. Intermittent insufficiency in the vertebral-basilar system.
2. Intermittent insufficiency in the carotid system.
3. Thrombosis in the vertebral-basilar system.
4. Actively advancing occlusion in the carotid system.

The technique of treatment in their series was similar to that used in the present report, except that it was prolonged for six months or more in many cases. The results were contrasted with previous patients not treated, but no really controlled trial emerges. The authors believed that the anticoagulant therapy achieved a favourable result by decreasing attacks of intermittent insufficiency, and by stopping the progress of neurological deficit in advancing arterial occlusion. Most of the other recent work in North America has been in connexion with long-term anticoagulant therapy in cerebrovascular disease, and the immediate results in cerebral infarction cannot be determined from the data furnished in these reports; but in a paper on this form of treatment as a whole Fisher (1958) has described his experiences in treating 58 patients. Of these exactly half had cerebral infarction, 14 patients showing a gradual evolution and 15 a fully developed stroke. In the former group three patients progressed to severe paralysis, five showed a 'satisfactory result', and six a striking recovery. Interruption of anticoagulant therapy occurred in five of the 11 favourable cases, and in three worsening of the condition followed. Fisher rightly pointed out the absence of any comparative series, but was apparently impressed by the 'favourable effects of anticoagulants in patients whose condition was steadily deteriorating'. In the 15 patients with fully developed stroke the results were bad, and did not differ from his expected results in untreated patients. Fisher considered that his experience showed no evidence that anticoagulant drugs cause haemorrhage into infarcted brain. Visceral bleeding was encountered in only 10 per cent. of his patients, and of these six patients only two (four per cent.) bled seriously. In this country less enthusiasm has been shown for these drugs. Brain (1957) pointed out the importance and the difficulty of correct diagnosis, and said: 'undoubtedly there is a risk that anticoagulants may lead to a haemorrhage into such an infarcted area. Since it is doubtful whether they will in other respects do good, it would seem unwise to give anticoagulants within at least three weeks of an attack of cerebral infarction'. Personal experience, however, suggests that this risk is considerably less in practice than has been thought, and that no hesitation need be shown in giving anticoagulants to selected patients at the beginning of an attack of cerebral infarction.

On the Continent de Morsier and Tissot (1957) were also convinced that anticoagulants are contra-indicated in the acute phase of cerebral softening, and agreed with Brain that three weeks should elapse before they are given. They based their argument on the findings of Bruetsch (1955), who found no thrombus in 20 cases of cerebral infarction, and on the views of Mahoudeau, Daum, and

Dubrisay (1954), who suggested that bleeding might occur into areas of acute cerebral softening and might be aggravated by diminished coagulability of the blood. Again these arguments are founded on belief rather than experience.

It has been impossible to find an adequately controlled series of non-selected consecutive patients treated with anticoagulants for cerebral infarction, and therefore the natural history of this condition is at present of great importance. Probably Glynn's series (1956), already referred to, gives the best picture of results in unselected consecutive admissions to a large general hospital receiving patients from its own neighbourhood. Glynn's results correspond very closely with the present author's previous experience (Carter, 1959). In Glynn's series of 163 patients 46 per cent. showed a good or fair recovery, walking with the help of a stick, 17 per cent. showed a poor recovery or none at all, and 37 per cent. died; and in the present author's untreated series for 1952, out of 54 patients, 13 recovered, 12 improved, nine were unchanged, and 20 died; that is, 46 per cent. recovered or improved, 17 per cent. did not improve, and 37 per cent. died.

Vastola and Frugh (1959) have described their experiences in treating with anticoagulants patients suffering from recent cerebral infarction. They treated 55 such patients consecutively admitted to the King's County Hospital, New York City, of whom 41 were men and 14 women. The mean age was 67·6 years. The absence of a control series suggests that it was impossible to match their group adequately. They compared their results with 'certain generally accepted qualitative expectations'. Their diagnostic criteria and methods of treatment were very similar to those used in the present series, and they have added a valuable contribution in suggesting a search for bilirubin in the cerebrospinal fluid, so as to exclude still further the possibility of intracranial haematoma. They also divided their series into 'complete' (25 cases) and 'incomplete' (30 cases) categories; they gave anticoagulants for from one to four weeks, and assessed their patients four to eight weeks after therapy had begun. Of the 30 patients in the 'incomplete' group 22 were improved, and in the 'complete' group of 25 only six were improved. They considered, however, that this was 'the result expected in any group of patients with occlusive vascular lesions who received only general supportive care'. Five patients with incomplete neurological deficit became worse while receiving anticoagulants, and two of them died. One had a subarachnoid haemorrhage on the 17th day of treatment, when the prothrombin time was 2·2 times the normal; the other became stuporose on the fourth day, and developed bleeding from the mouth and haematuria on the sixth day. The prothrombin time was 4·2 times the normal, and the cerebrospinal fluid was clear, but contained excess of bilirubin. It was thought that bleeding had occurred into the infarct shortly after admission to hospital. No autopsy studies were available in these two cases. Autopsies on four patients with complete hemiplegia showed that in two cases massive intracerebral haemorrhage had occurred about three days after the onset of the stroke, during anticoagulant therapy. The authors concluded that in their hands the risk of haemorrhage into the brain appeared to

contra-indicate the use of anticoagulants in the treatment of acute cerebrovascular lesions.

In view of the above advice against anticoagulants, it is necessary to study the results of any series with care. It appears that anticoagulants have not improved the natural history of sudden cerebral infarction (Fisher, 1958; Carter, 1959) when administered in the accepted dosage. It is also evident from the results of the present study that the overall prognosis of slow-onset cerebral infarction is slightly improved, and that, although the control series is well matched, the difference is not quite statistically significant. If, however, the patients are further selected so that anticoagulants are used only for those whose neurological deficit is not complete at the beginning of treatment, improvement, in comparison with similar patients not treated, seems to be statistically confirmed. Difficulty arises when a patient is first seen in hospital with an incomplete lesion due to cerebral infarction, because it is impossible to say immediately whether the deficit will progress. Perhaps nothing will be lost by waiting until evidence of extension of the infarction shows itself, and, although the general results of untreated incomplete lesions are not impressive (Carter, 1959), no prognostic difference could be linked to the time of commencing treatment. This difficulty is very like that encountered in cardiac and pulmonary infarction, where a 'mild' infarction may be the precursor of much greater trouble, and this possibility cannot be gauged by any clinical method or scientific test. No physician, however, likes to embark on a potentially dangerous and bothersome treatment until he is sure that the patient is likely to get worse without it, and unless he can see evidence of worsening a wise and natural conservatism will prevail. Particularly is this so if the slightest improvement occurs in the patient while under observation.

The evidence put forward in this report suggests that selection of patients suffering from cerebral infarction is important before considering anticoagulant therapy. Only those patients whose stroke is of gradual onset, and whose history suggests progressive neurological deficit, or who show signs of this progression while under observation, are suitable for anticoagulant therapy. Severe hypertension, with a diastolic reading over 120 mm. Hg, is considered a contra-indication to treatment, owing to the increased incidence of complications in such patients and the greater frequency of haemorrhagic infarction and intracerebral haematoma. Other contra-indications are a history of haematemesis or prolonged dyspepsia suggesting peptic ulceration, evidence of hepatic disease, and loss of consciousness.

I am greatly indebted to Sir Charles Symonds for his interest and his comments on this report. The secretarial expenses of the investigation were defrayed by a grant from the Research Committee of the North-West Metropolitan Regional Hospital Board.

Summary

1. Ninety patients with ingravescent cerebral infarction have been studied.

This condition is defined as cerebral infarction of gradual onset in which the neurological lesion is still incomplete after not less than two hours.

2. Alternate patients were treated with anticoagulants for four weeks, leaving the other 45 as a control series.

3. Diagnostic criteria are discussed, particularly with reference to differentiation from intracranial haematoma.

4. The results have been analysed, and it is suggested that further selection of patients is necessary. The best results, and the only significant figures as regards improvement, were obtained in patients whose lesion was incomplete at the beginning of treatment when compared with similar patients untreated.

5. The dangers of anticoagulant treatment are discussed. Although important, they were not a cause of anxiety in the present series. Nine patients (20 per cent.) had a total of 17 minor haemorrhagic episodes; of the eight patients in the treated group who died, only one showed any haemorrhage at autopsy. This haemorrhage was due to an unsuspected meningioma which ruptured the cavernous sinus.

6. It is suggested that anticoagulant therapy is at present the treatment of choice in patients suffering from ingravescent cerebral infarction if the neurological deficit is not complete by the time treatment can be started. This treatment seems to be comparatively free from risks if patients with severe hypertension and those with loss of consciousness are excluded.

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THE ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

1960

FIFTY-FOURTH ANNUAL GENERAL MEETING

THE FIFTY-FOURTH ANNUAL GENERAL MEETING was held at The London Hospital on Friday and Saturday, May 27 and 28. The attendance book was signed by 274 members and 40 visitors.

The President, Professor Harold Scarborough, was in the Chair.

The Minutes of the last Annual General Meeting, having been published in the *Quarterly Journal of Medicine*, were taken as read, confirmed, and signed. The following Officers, Executive Committee, and Senior and Ordinary Members were elected unanimously, as was the new member of the Editorial Board:

Executive Committee

President: Dr. Donald Hunter.

President-Elect: Professor Bruce Perry.

Hon. Treasurer: Dr. C. M. Fletcher.

Hon. Secretary: Dr. R. I. S. Bayliss.

Members for England and Wales:

Dr. C. N. Armstrong.
Professor A. Kekwick.
Professor Melville Arnott.
Dr. R. Bodley Scott.
Dr. Charles Baker.
Dr. S. R. F. Whittaker.

Members for Scotland:

Dr. J. H. Wright.
Professor R. B. Hunter.
Professor K. W. Donald.

Members for Ireland:

Dr. M. G. Nelson.
Dr. S. Dundon.
Dr. M. I. Drury.

Election of Senior Members

Dr. William Evans.
Professor Stanley Graham.
Dr. T. K. MacLachlan.
Dr. R. H. Micks.
Dr. T. R. R. Todd.

Election as Member of the Editorial Board

Dr. J. D. N. Nabarro.

Election of Ordinary Members

John Anderson, M.D., M.R.C.P., Assistant Director of the Department of Medicine, King's College Hospital Medical School.

John Reginald Bignall, M.D., M.R.C.P., Physician, Brompton Hospital.

John Michael Bishop, M.D., M.R.C.P., Senior Lecturer in Medicine, University of Birmingham.

Alexander Stuart Douglas, M.D., M.R.C.P., Senior Lecturer in Medicine, University of Glasgow.

John Maurice French, M.D., M.R.C.P., Physician in Gastroenterology, United Birmingham Hospitals.

David Geraint James, M.D., M.R.C.P., Physician, Royal Northern Hospital, London.

Thomas Davidson Veitch Lawrie, M.D., Assistant Physician, Royal Infirmary, Glasgow.

Edward Lawson McDonald, M.D., M.R.C.P., Assistant Director, Institute of Cardiology, University of London.

Malcolm MacLeod, M.B., F.R.C.P.Ed., Senior Lecturer in Medicine, University of Aberdeen.

Walter Bryan Matthews, M.R.C.P., D.M., Consultant Neurologist, Derbyshire Royal Infirmary.

William Stanley Peart, M.D., F.R.C.P., Professor of Medicine, St. Mary's Hospital, London.

Richard Douglas Tonkin, M.D., F.R.C.P., Physician, Westminster Hospital.

John Vallance-Owen, M.D., M.R.C.P., Senior Lecturer in Medicine, King's College, University of Durham.

Election of Overseas Ordinary Members

Robert Bews Kerr, M.D., F.R.C.P., Professor of Medicine, University of British Columbia.

Hugh Vivian Morgan, M.B., F.R.C.P., Professor of Medicine, University of Khartoum.

The Treasurer, in presenting the accounts, said that the Association's funds had been reinvested to provide a higher interest. A sum of £350 had been given to the *Quarterly Journal of Medicine* to speed the publication of papers already accepted.

The Chairman of the Editorial Board, Dr. A. M. Cooke, explained that in 1959 an unusually large number of manuscripts had been submitted, and of good quality, so that a large amount of material awaited publication. The position had been aggravated by the printing strike in the summer of 1959. Several papers submitted towards the end of 1959 were in danger of not being published until 1961. The Editors felt that there were two problems: first the unusually large amount of material now in hand, and secondly the fact that the number of suitable papers submitted seemed to be slowly but steadily increasing. The Executive Committee had generously recommended a subvention of £350 to help with the former problem. As regards the latter, the Editors had instituted a policy of stricter editorial standards and had considered the question of a permanently larger journal. If the present standard size of 576 pages (36 sheets) were increased to 608 or 640 pages (38 or 40 sheets), the Clarendon Press would advise a price to subscribers of 75*s*. and to members of the Association of 50*s*. The increases in price of the Journal since the war were as follows:

	Subscription price	*Price to members of the Association*
Pre-war to 1951	35*s*.	25*s*.
1952	40*s*.	28*s*. 6*d*.
1956	50*s*.	35*s*.
1959	60*s*.	42*s*. 6*d*.

The present price was less than twice the pre-war figure, and an increase to 75*s*. would be little more than twice that figure.

As a change in the price of the Journal to members of the Association required an alteration of the by-laws, of which due notice had to be given, it would not be possible to make any change until the Annual General Meeting of 1961. The Editors hoped that there might be an increase in the standard size of the Journal from January 1962 and that in the meantime the Association would consider sympathetically making a further subvention for 1961 if this was thought necessary. After a general discussion it was resolved to leave the Executive Committee to make recommendations as to an increase in subscription at the next Annual General Meeting.

Place of Future Meetings. Professor Bruce Perry said that the meeting in Bristol would be held on April 14 and 15, 1961. The Association would meet in Birmingham in 1962, Dundee in 1963, Oxford in 1964, and London in 1965.

The President paid tribute to Dr. Marriott, who was resigning from the Editorial Board after giving 14 years' invaluable service.

The newly elected President, Dr. Donald Hunter, then took the Chair.

SCIENTIFIC BUSINESS

Friday Morning, May 27

1. A characteristically spirited and illustrated account of the history of *Stepney and The London Hospital* was given by DR. DONALD HUNTER.

2. *The Pattern of Mitral Valve Disease in Southern Nigeria* was described by DR. D. G. ABRAHAMS (introduced by PROFESSOR C. WILSON) as having several unusual features. Stenosis was uncommon; combined valvular lesions were rare, and much the most common lesion was mitral incompetence accompanied by severe pulmonary hypertension. A series of 50 cases of this syndrome was described. X-rays consistently showed a small aortic knuckle, much enlargement of the right ventricle and pulmonary arteries, and some hypertrophy of the left ventricle. Left atrial enlargement was never great, but the right atrium sometimes became aneurysmal. The electrocardiogram showed biventricular enlargement with very large right atrial P waves which were sometimes notched. Arrhythmias, except ventricular extrasystoles, were very rare. The pulmonary artery pressure could be high (systolic 100 mm. Hg or more) and this seemed due in part to back-pressure and in part to vascular resistance, although little vascular damage in the lungs could be demonstrated histologically or by injection studies.

Two distinct processes—rheumatic and endomyocardial fibrosis—were found at autopsy, and in several instances both were present. Rheumatic lesions affected mainly the ventricular myocardium and endocardium, the valves being remarkably spared. Rheumatic mitral incompetence was produced by fibrosis of the papillary muscles and chordae tendineae, with dilation of the valve ring from left ventricular dilatation. Endomyocardial fibrosis started at the apex of the left ventricle and spread up the inflow tract, involving the posterior papillary muscle and sometimes plastering down the mitral cusp and rendering the valve incompetent. The outflow tract of the left ventricle was never involved. The clinical picture produced by these two processes was identical, but endomyocardial fibrosis of the left ventricle could be distinguished from rheumatic mitral incompetence by the shape of the left ventricular pressure curve which showed a dip-and-plateau pattern in the former condition. The aetiology of endomyocardial fibrosis was obscure, and DR. ABRAHAMS suggested that perhaps it was a 'final common pathway' type of response to various cardiac insults in a heart rendered susceptible by constitutional, dietary, biochemical, or genetic factors. In Nigeria the commonest cause might be rheumatism.

PROFESSOR MELVILLE ARNOTT said that heart disease of similar type seemed to occur in many, perhaps all, parts of Equatorial Africa. Recently in the tropical zones of South America he had learnt of the high incidence of a chronic myocarditis with endomyocardial fibrosis due to *Tr. cruzi* (Chagas disease). It was necessary to be cautious in applying the label 'rheumatic' to the West African cases; mitral stenosis did not occur, nor did auricular fibrillation, and the only real points in common with rheumatic carditis, as seen in Great Britain, was the finding in some cases of Aschoff bodies and high antistreptolysin titres—features which could be reactions to some pathogenic agent other than the β-haemolytic streptococcus. He asked how often streptococci were found in the fauces or in wounds in West Africa.

DR. ABRAHAMS replied that haemolytic streptococci were very rarely isolated from the throats of these patients, but this might be due to the examination being made months after the onset of the illness. Other portals of entry—particularly tropical ulcers—might be significant. It was not surprising that auricular fibrillation was so uncommon, because this was a severe complication and the patient might die before reaching hospital. It was possible that this unusual form of rheumatic mitral incompetence occurred in England during the eighteenth and nineteenth centuries.

DR. HUTTON commented that in Kampala endomyocardial fibrosis was considered a final common pathway, the result of several different diseases.

PROFESSOR K. W. DONALD thought that the pulmonary artery pressure was unduly high for uncomplicated mitral incompetence, but DR. ABRAHAMS said that the pulmonary hypertension was caused by mitral incompetence in the presence of a left auricle which was hypertrophied and not dilated. The mean left atrial pressure could be as high as 20 mm. Hg, and this was transmitted retrogradely to the pulmonary veins.

DR. G. DE J. LEE asked whether there was any correlation between the long-term nutritional state of the patient and the cardiac lesion. In reply Dr. Abrahams said none of the patients showed signs of malnutrition when first examined, but this did not mean

that severe protein deficiency had not occurred 10 to 20 years before when they were children.

3. Dr. J. O'Sullivan, Dr. M. G. FitzGerald, Dr. J. D. Blainey (introduced), and Dr. J. Malins discussed *Proteinuria in Diabetes*, and reported that among 3,841 current attenders at a diabetic clinic 547 had protein in their urine. Relative to the numbers at risk proteinuria was most common in young male patients, and commoner in women than in men at all other ages. The known duration of diabetes before the onset of proteinuria became progressively shorter with increasing age at diagnosis, and many of the older patients had proteinuria at the time of diagnosis. In a study of 100 patients—a representative sample of the total with proteinuria—it was found that 82 had diabetic nephropathy, 73 having nephropathy alone and nine a combination of nephropathy and urinary-tract infection. In only two patients was the proteinuria caused by infection alone. Renal biopsies done on a number of patients showed that the histological changes of diabetic nephropathy were usually more advanced than the clinical picture suggested. No significant difference was found in the incidence of urinary tract infection, as determined by quantitative bacterial counts on urine cultures, between the patients with proteinuria, 100 diabetics without proteinuria, and 100 non-diabetic controls of similar age and sex distribution—the incidence in the three groups being about 11 per cent. Among the patients with nephropathy the classical Kimmelstiel–Wilson syndrome was rare, and the nature of the proteinuria as determined by electrophoretic and immune chemical clearances seemed non-specific. Renal biopsy in diabetics without proteinuria showed a surprisingly high incidence of diabetic renal disease, including histological changes in the kidneys of three out of nine patients with no demonstrable retinopathy. The presence of histological changes in the kidney of a 15-year-old girl, with diabetes of acute onset 18 months before, suggested that diabetic renal disease may occur even in diabetes of relatively recent onset.

4. Dr. G. F. Adams and Dr. J. D. Merrett (introduced) reviewed *Hemiplegia* in 736 patients (314 men, 396 women, and 26 untraced), who had been admitted for rehabilitation to the geriatric wards of the Belfast City Hospital two weeks or more after onset, and who therefore represented the hard-hit survivors of strokes, not the general run of those admitted to hospital. Three groups were defined—those who recovered independence (subdivided into two grades), those who became chronic invalids (having failed to walk unaided after three to six months attempted re-training), and those who died within two months of onset. Although 81 per cent. of the patients survived the next two months, their chance of being able to get about and look after themselves (42 per cent.) was little better than that of becoming relatively helpless invalids (39 per cent.). No age differences were found between men and women within these groups or between the grades of recovery, but age did affect the outcome, those who died being on average older than the chronic invalids who, in turn, were older than those who recovered. As might be expected, the earlier physical re-training began the higher the proportions of recoveries. Contrary to general belief, recoveries included a significantly greater proportion of men with dominant hemisphere lesions, and the same trend was evident amongst the women. Lesions of the left side of the brain are said to carry an adverse prognosis because of speech difficulties and loss of preferred limbs. Dr. Adams thought that the more intensive and prolonged physical re-training now used may have encouraged better compensatory efforts with the unpractised left arm and leg than was formerly possible with left cerebral lesions, whereas patients with right cerebral lesions often have an even greater handicap than aphasia in bizarre disturbances of body-image. Survival times of recovered and long-stay patients were compared by life-table analysis; in each age and admission group those who recovered lived longer than those who became chronic invalids, and women survived somewhat longer than men. Apparently 50 per cent. of patients who recover from a stroke will survive at least six years if aged less than 65 at onset, or about three and a half years if men, or four years if women, over that age.

Dr. J. Marshall asked whether the equally good results of rehabilitation in patients with lesions in the dominant and non-dominant hemispheres were due to there being few patients with dysphasia. Dr. R. W. D. Turner inquired whether Dr. Adams had any special techniques for rehabilitating these patients beyond those in general use.

In reply, Dr. Adams reiterated that body-image disturbance in the non-dominant hemisphere lesion was often a greater handicap than speech defect. There were no shortcuts in the management of these patients, the essentials being to await the slow improvement always to be expected, and to provide an environment which would encourage the patient to make the most of his functional recovery. Details of the techniques were available in the current issue of the *British Journal of Clinical Practice*.

5. The investigation of *Thyrotoxicosis and Thyroid-Stimulating Hormone* was discussed by DR. D. S. MUNRO, DR. P. W. MAJOR (introduced), and PROFESSOR G. M. WILSON, who had measured thyroid-stimulating hormone (T.S.H.) in human serum by the release of ^{131}I-labelled hormone from the mouse thyroid (McKenzie, 1958). International Standard T.S.H. and serum from patients with myxoedema caused a peak increase in circulating radioactivity in mice three hours after intravenous injection. In contrast, the injection of serum from 31 out of 42 patients with thyrotoxicosis was followed by a delayed response which did not reach a maximum until 12 hours or later. Although there was great variation in the size of response, no correlation was found with such factors as age, sex, type of thyroid gland enlargement, or the severity of associated eye signs. In addition to this difference in its time of peak effect, the circulating thyroid-stimulating activity in thyrotoxicosis was associated with several different protein fractions, whereas in myxoedema T.S.H. was confined to the gamma-globulin. T.S.H. extracted from normal human pituitaries resembled the International Standard, and the early peak effect was not altered by solution in serum which caused a delayed response. When serum from a patient with thyrotoxicosis was injected into mice subjected to hypophysectomy after being prepared for T.S.H. assay, the delayed response was the same as in intact animals. No difference was detected in the thyroid-stimulating activity of serum samples withdrawn simultaneously from the internal jugular and forearm veins of patients undergoing thyroidectomy for thyrotoxicosis. Eight patients successfully treated by operation or radio-iodine were all found to have increased circulating thyroid-stimulating activity after recovery. Yet the T.S.H. extracted from the pituitaries of three patients known to have suffered from thyrotoxicosis followed the same time course as the International Standard. Serum which caused a delayed response in measurements of radio-iodine discharge stimulated the thyroid uptake of ^{131}I in mice, and produced the histological appearances of increased thyroid activity. It was concluded that these experiments establish the existence of a circulating activator of thyroid function in thyrotoxicosis which may well be of aetiological importance.

In reply to PROFESSOR G. M. BULL, who asked whether T.S.H. could be detected in normal sera, DR. MUNRO said the method was not sufficiently sensitive.

PROFESSOR A. G. MACGREGOR commented that one would expect the mother of a child with the rare condition of congenital hyperthyroidism to have very high circulating levels of thyrotrophic hormone, as it was believed that the condition was due to transplacental passage of maternal T.S.H. DR. MUNRO said that one of the most striking examples of the delayed response was elicited by serum from a patient seven years after having a successful partial thyroidectomy for thyrotoxicosis. Since operation she had given birth to two children, who both had congenital thyrotoxicosis. Maternal serum had been examined on several occasions during the year subsequent to birth of the second child, and had consistently shown high thyroid-stimulating activity.

In answer to PROFESSOR RUSSELL FRASER, DR. MUNRO said that the delayed type of response had been detected in the sera of patients with thyrotoxicosis and nodular goitres of long standing, in addition to those with Graves' disease.

Reference: McKenzie, J. M. (1958) *Endocrinology*, **62**, 372.

6. *The Circulatory Effects of Antihypertensive Drugs* had been studied by DR. S. H. TAYLOR (introduced) and PROFESSOR K. W. DONALD by cardiac catherization in patients with uncomplicated essential hypertension, whose ages ranged from 30 to 55 years. Systemic pressures were measured directly in the ascending aorta, and the cardiac output was determined by the Fick principle. Observations were made in the supine position at rest, during light work, during heavier work, and in the recovery phase 15 to 20 minutes after stopping exercise. In 16 patients 4 to 32 mg. of pentolinium was then injected intravenously, and all the observations repeated. Before giving the drug the resting cardiac output, and the response of the cardiac output to exercise, were normal. The systemic circulatory effects of the drug at rest were a moderate reduction of cardiac output and a considerable reduction in systemic vascular resistance, with a fall in blood-pressure. During exercise after the drug was given, the cardiac output response was severely impaired and largely unaccompanied by any further reduction in systemic vascular resistance, the blood-pressure increasing slightly although still appreciably reduced.

Six patients were studied by similar techniques before and after the oral administration of chlorothiazide, given in a dose of 1 g. daily supplemented by oral potassium and constant sodium intake of 75 m-equiv. per day. After 14 days' treatment with chlorothiazide

the patients were studied again before and after pentolinium. The circulatory effects of chlorothiazide alone were moderate reductions in the resting cardiac output, the systemic vascular resistance, and the blood-pressure—effects which persisted during exercise. The influence of chlorothiazide upon the response to pentolinium was only quantitative, the patients showing the same reduction in blood-pressure and other haemodynamic effects as after pentolinium alone, but at a much lower dose range of pentolinium. Chlorothiazide caused a contraction of the plasma volume (measured with radio-albumin) of about 0·5 litre.

A third group of nine patients was studied before and three months after receiving reserpine in an oral dose of 0·75 mg. daily. The effects of reserpine were the most 'physiological' of all the drugs studied, in that the fall in the resting blood-pressure was maintained during exercise, and was due to a decrease in the systemic vascular resistance without any change in the resting cardiac output or in the response of the cardiac output to exercise.

A fourth group of 16 patients was studied before and after the intravenous injection of 30 to 600 mg. bretylium. At rest, the effects of the drug upon the blood-pressure were variable, most patients showing a slight or moderate reduction, but a few a slight increase. The reduction in the resting systemic vascular resistance which followed the intravenous injection of bretylium was accompanied in nearly all cases by an increase in cardiac output of about 0·7 l./min./sq. m. After the drug the cardiac output response to exercise remained within normal limits, but there was a progressive reduction in the systemic vascular resistance, causing a considerable fall of blood-pressure on exercise. Bretylium consistently produced a considerable elevation of the pulmonary vascular resistance, which at rest ranged from 50 to 450 per cent. of the previously normal values, without any important change in pulmonary wedge pressure, pulmonary blood-flow, respiratory rate, or ventilatory volumes. This increase in pulmonary vascular resistance persisted during exercise.

Professor O. L. Wade asked whether Dr. Taylor had any information on the mechanism by which these hypotensive drugs altered the distribution of blood-flow during exercise. Dr. Taylor said that during these studies the blood-flow in various regions of the body had been measured. That to the exercising legs and to the brain had not changed after bretylium. The blood-flow through the splanchnic area on exercise was much less after bretylium than before it, and renal blood-flow was also greatly reduced on exercise. Observations on the blood-flow through the arm muscles, however, suggested that the fall in blood-pressure on leg exercise after acute administration of bretylium was due to a greatly increased flow through the large mass of non-exercising muscle.

Dr. D. Kerr remarked that the interpretation of the data on reserpine and chlorothiazide was complicated by the patients being rested in hospital between the first and second observations, and asked whether the effect of bed rest alone had been studied. Dr. Taylor replied that this had not been done, and in fact the patients had not been confined strictly to bed.

In answer to Professor Sir Robert Platt he said that none of the patients had suffered any adverse effects from the exercise. In reply to Professor T. B. Counihan he said that the response to bretylium had been assessed with the patient only in the supine position, and the effect of posture had not been studied. Dr. J. C. Gilson inquired whether any measurements had been made after prolonged treatment with pentolinium or bretylium, and Dr. Taylor said this was being investigated.

Dr. P. Reynell asked whether the effects of guanethidine were the same as those of bretylium, because both occasionally induced dizziness and hypotension on exertion. Dr. J. Shillingford said that he thought both drugs induced similar effects; guanethidine seemed to reduce peripheral resistance with comparatively little effect on cardiac output, and the hypotensive effect in some cases was further increased by a reduction in peripheral resistance on exercise.

After lunch, kindly provided by the Board of Governors of the London Hospital, the afternoon was devoted to the study of a large number of scientific demonstrations.

Annual Dinner

The Annual Dinner was held in the Egyptian Hall of the Mansion House, the London Members kindly providing sherry beforehand. The President, Dr. Donald Hunter, was in

the Chair. He proposed the Royal Toast, welcomed the Lord Mayor and the other guests, and spoke about the Association. The Lord Mayor, Sir Julian Huxley, and Lord Birkett replied. Professor Sir Derrick Dunlop spoke warmly of the President.

Saturday Morning, May 29

7. Dr. Alice Stewart spoke on *Preconception Leukaemias*. Examination of official statistics of mortality and the records of a recent survey of childhood malignancies had revealed two aetiologically distinct varieties of leukaemia. One variety (preconception leukaemias) was inherited from apparently healthy parents, and produced malignant stem cells indistinguishable from lymphoblasts. Preconception leukaemias were responsible for the early peak of leukaemia mortality, and the increasing incidence was due to antibiotics having reduced the number of premature deaths from acute infections. The basic lesions of preconception leukaemias might involve other systems, and occasionally produced both mongolism and leukaemia. The aetiological factors responsible for preconception leukaemias had been sought in the previous generation, the relevant clues being old parents, early miscarriages, and mongolism. Postconception leukaemias were acquired during the lifetime of the affected individual, and were relatively uncommon in childhood. They may, however, be caused by prenatal X-rays, and possibly by rubella. There may also be a connexion between these cases and threatened abortions. When postconception leukaemias developed in childhood the cell type depended on the date of the initial lesion. Lesions acquired within five months of conception produced stem cells, whereas lesions acquired later produced granulocytes or lymphocytes. The latent interval of childhood leukaemias varied with age. The average for preconception leukaemias was about four years, and for postconception leukaemias arising shortly before birth nearly twice as long. The preponderance of boys among childhood leukaemias was due to secondary influences, such as pneumonia and fractures, both of which hastened the onset of symptoms. The several causes of leukaemia may have in common the fact that they damage a specific chromosome.

Professor L. J. Witts said that the concept that a malignant disease could be due to preconceptional influences was of great importance, as hitherto this idea had been applied only to the sporadic occurrence of inheritable diseases such as haemophilia. He felt that current data on the frequency of different types of acute leukaemia should be treated with great reserve. In a recent trial, in which a group of expert haemotologists had examined the same slides 'blind', the diagnoses had differed greatly. Moreover, the same individual would frequently give a different diagnosis when presented with the same slide on a second occasion.

Dr. C. A. Clarke asked whether there was any concentration of leukaemia in the parental generation of mongol children, because at least one case had been reported in which the chromosome complement of the mongol was normal, whereas the healthy father was trisomic.

Professor D. A. K. Black stigmatized the new term 'preconception leukaemia' as anachronistic, suggesting 'preconception leukaemogenesis' as a clumsier but more accurate alternative; none the less these verbal preconceptions had not prevented his appreciation of Dr. Stewart's paper.

Dr. J. B. Rennie had had in his care two pregnant women with acute leukaemia, one of whom was delivered of an apparently normal infant by Caesarean section, and he wondered whether there was an increased liability to leukaemia in such infants.

8. *The Anti-Gamma Globulin Consumption Test with Special Reference to Hashimoto's Disease* was described by Dr. E. J. Field and Dr. A. Ridley (introduced by Dr. H. Miller). This test, designed to demonstrate circulating thyroid antibody, depended upon the ability of a tissue to which antibody has become fixed to reduce the titre of a Coombs' serum coming in contact with it. A given volume of serum (five drops from a standard pipette) was incubated at 38° C for half an hour with $15{\cdot}0 \pm 0{\cdot}2$ mg. of finely divided normal thyroid substrate, washed eight times to remove blood contamination. Antibody in the serum became fixed to the substrate, which was then again washed eight times in the cold, to free it from non-antibody globulin. Ten drops of 1:64 Coombs' serum from a standard pipette were added to each of the washed thyroid substrates, and the tubes incubated for about 15 minutes at 38°. This enabled any antibody fixed to the substrate to react with the Coombs' serum and so reduce its titre. Six specimens were processed simultaneously —one being a control of healthy blood-donor serum. The Coombs' sera were recovered by

centrifugation, and titrated out at doubling dilutions to 1:1,024. The control-specimen titre might diminish by half a dilution as compared with the original Coombs' serum, i.e. a 'basic consumption' of half a tube occurred.

One hundred 'blind' sera had been tested. Fifty-four of these turned out to be controls: four gave false positives, but two were negative on repetition; of the remaining two, one was weak, and the other was from a case of disseminated lupus erythematosus. Eighteen specimens were from Hashimoto's disease with a positive tanned red-cell test, and 16 were found positive. Fifteen specimens were from Hashimoto's disease with a negative tanned red-cell test, and 10 of these were positive by the A.G.C. test (four strongly, three medium, and three weakly). Seven cases of myxoedema, all with a positive tanned red-cell test, gave positive A.G.C. tests. The method appeared to be a useful diagnostic and research adjunct in thyroiditis.

PROFESSOR DOUGLAS HUBBLE asked whether the results of the anti-gamma globulin consumption test had been correlated with the complement fixation test, and DR. C. A. CLARKE inquired if the test was positive in athyreotic cretinism.

In reply, DR. RIDLEY said that the number of thyroid sera in PROFESSOR SMART'S 100 'blind' sera, on which the complement fixation test had been performed, was too small to allow any correlation with the results of anti-gamma globulin consumption test. Patients with cretinism had not been studied.

9. *Pseudoxanthoma Elasticum* (P.X.E.) was described by DR. G. M. BERLYNE (introduced) and PROFESSOR SIR ROBERT PLATT as a rare recessive disease in which there was widespread degeneration of elastic tissue, giving rise to the clinical manifestations of angioid streaks in the retina, characteristic cutaneous changes, and arterial degeneration. An investigation had been made into the families of five unrelated patients suffering from typical P.X.E. in order to determine whether the heterozygote was clinically detectable. In the first family the sister of the proposita was found to be suffering from typical P.X.E., the unaffected brother and father of the patient having abnormally visible choroidal vessels. The mother was normal. In the second family the father of the propositus had abnormally visible major choroidal vessels in both retinae, in the absence of angioid streaks. His skin was normal. He had three children, all of whom had the same retinal anomaly. The twin children of the propositus also had abnormally visible major choroidal vessels, his other child being quite normal. In the third family one of the three children of the proposita was found to have abnormally visible choroidal vessels. In the fourth family the same anomaly was found in three generations, and in the fifth in both parents and the sister of the proposita. It was concluded that the presence of abnormally visible choroidal vessels was indicative of the heterozygous form of P.X.E., although penetration was often incomplete.

Examination of these cases, and of case reports from the literature and from colleagues, showed that of 22 families of two or more sibs in which complete sibships were recorded, 21 showed either male or female members affected, but not both. Such a finding was strongly indicative of partially sex-linked inheritance, i.e. a recessive gene carried on the homologous portions of *X* or *Y*, a condition not yet certainly known to occur in man. There were, however, some indications from consanguineous matings that the proof of this was not as sound as it seemed at first sight.

PROFESSOR DOUGLAS HUBBLE asked what was the frequency of abnormal choroidal vessels in the general population, and DR. BERLYNE replied that in a survey of 200 normal people no abnormally visible vessels had been seen in non-myopic subjects. One sibship, however, had been found by PROFESSOR SIR ROBERT PLATT, in a survey of identical twins, in which there were these abnormal vessels without a family history of P.X.E.

PROFESSOR R. E. TUNBRIDGE doubted whether the skin lesion was due to an abnormality of elastic tissue. In normal skin only 2 per cent. of the fibres were elastic. Abnormal collagen stained readily with the standard elastic stains, and three specimens of skin from this condition had been found to have abnormalities of the collagen in so far as their reaction to enzymes and alkalis were concerned. Normal collagen acted on by collagenase or by alkalis was grossly altered, and then took up elastic stains. DR. BERLYNE replied that the term 'pseudoxanthoma elasticum' had been used only for want of a better one, and he had deliberately avoided any discussion about the aetiology of the condition.

In reply to PROFESSOR JOHN CROFTON, DR. BERLYNE said that P.X.E. rarely caused complete blindness, although often macular vision was lost, the patient being unable to read but able to avoid large objects. DR. BERNARD SCHLESINGER said that calcification was

sometimes seen in the peripheral arteries of patients with P.X.E., and asked whether relatives of these patients had been found to have hypertension, but DR. BERLYNE had not observed this.

DR. J. F. STOKES welcomed the use of the initials P.X.E., because the condition did not resemble xanthoma, and the doubts as to whether elastic tissue was in fact involved meant that the disease should perhaps be called 'pseudoxanthoma pseudoelasticum'. One of the chief advantages of initials was that what they stood for could be forgotten, sometimes quite fast, and they were preferable until the condition could be christened rationally.

10. DR. D. G. PENINGTON (introduced by PROFESSOR C. WILSON) discussed *The Plasma Erythropoietic Factor and its Role in Anaemia and Renal Disease*. The concept of humoral regulation of erythropoiesis dated from 1906, but a convincing direct demonstration of a hormone specifically stimulating erythropoiesis came only in 1953 and 1954. Since that time evidence had been presented suggesting a renal origin of this hormone. However, most of the recent studies of its incidence in anaemia had been based on assay procedures using hypophysectomized or starved animals, and these were open to grave criticism on grounds of specificity. The polycythaemic rat was used in this study as the recipient animal, and acceleration of erythropoiesis measured by ^{59}Fe utilization following injection of plasma from anaemic subjects. A further analysis of this assay procedure was presented, and it was claimed that this was the most specific of the procedures available, suitable for application to clinical problems. Erythropoiesis-stimulating activity was demonstrated in the plasma of patients with haemoglobin values of less than 50 per cent. (in conditions with both hypoplastic and hyperplastic marrow), the only instances in which such activity was not demonstrated being in severe anaemia associated with chronic renal disease. Chemical concentration of the hormone from plasma could be achieved without loss of activity, and by this means it was demonstrated that in such patients the hormone was still present in greater than normal amounts, although very much less than was found in other types of anaemia of comparable severity. It was concluded, therefore, that the anaemia of chronic renal disease could not be attributed solely to lack of this hormone, but that the low titres may be an important aetiological factor in the anaemia.

DR. D. VEREL asked whether any observations on the serum levels of haemopoietin had been made in patients with chronic Bright's disease who had had a recent haemorrhage. During a study at the London Hospital on the anaemia in Bright's disease it had been surprising to find a normal haemopoietic response to haemorrhage in two patients. DR. PENINGTON replied that the information to explain these observations was not yet available.

DR. P. HUGH-JONES asked whether studies on the amount of renal erythropoietic factor had been made in emphysematous patients and related to their degree of arterial oxygen desaturation, because it had long been a mystery why some hypoxic patients with emphysema became polycythaemic, whereas others did not. DR. PENINGTON said that increased titres of the hormone had been found in two patients with emphysema and secondary polycythaemia, and further studies in this field were continuing.

PROFESSOR T. B. COUNIHAN asked whether any observations had been made in polycythaemic patients with a hypernephroma or hydronephrosis. DR. PENINGTON said he had not had an opportunity to study such patients, but urged caution in interpreting reports of assays on renal vein blood based on a reticulocytosis in rats, because plasma from patients with both primary and secondary polycythaemia would produce a reticulocytosis, although plasma only from the latter contained the 'renal' hormone.

DR. T. A. J. PRANKERD asked whether an increase in red-cell volume had been observed after injections into rats, because the increased uptake of radioactive iron might only reflect a redistribution of this isotope throughout different iron pools in the body. DR. PENINGTON pointed out that Borsook had shown elevation of red-cell volumes in rats following the injection of similar extracts, but the quantities of plasma required to produce such changes precluded the use of this parameter for routine assays as opposed to the present use of radio-iron.

11. DR. D. J. FONE (introduced) and DR. W. T. COOKE discussed *Jejunal Biopsy in Adult Coeliac Disease and Allied Disorders*. Histological abnormalities had been described in many patients with 'idiopathic steatorrhoea', but it was not clear that the various lesions simply represented different stages of one pathological process. Sixty-eight patients with 'idiopathic steatorrhoea' had therefore been studied, and the histological findings at

jejunal biopsy correlated with clinical and laboratory features and the absorption of radioactive B_{12}, by means of the hepatic surface counting technique.

In 33 patients the jejunal mucosa had no villi, a 'flat' surface, disordered epithelium, and mild cellular infiltration. In general these patients presented chronic diarrhoea, malaise, and loss of weight. Anaemia was mild and rarely megaloblastic; abdominal pain was rare. Folic-acid excretion tests and xylose absorption tests were abnormal, and achlorhydria rare. Eighteen of the 21 tested had normal ^{58}Co–B_{12} absorption. In 31 patients the mucosa had villi, but these were abnormal in form; epithelial disorder was less severe, and cellular infiltration frequently heavier. In these patients diarrhoea was less common, but abdominal pain and severe anaemia more common; 18 presented megaloblastic anaemia of short duration. Of these 18, eight responded to B_{12} therapy; they had achlorhydria, and in four there was a deficiency of intrinsic factor. Ten responded to folic acid; they had free acid, and all except one absorbed B_{12} normally.

It was concluded that there were at least two aetiologically separate entities responsible for 'idiopathic steatorrhoea'. The differences in symptoms and duration of illness, especially the different incidence of severe anaemia, were against the lesion with 'abnormal villi' being either an earlier less severe stage, or the regenerated stage of the lesion with a 'flat' mucosa. It was suggested that the terms 'coeliac disease' and 'adult coeliac disease' should be confined to those patients with a 'flat' upper intestinal mucosa, and that those with 'abnormal villi' represented a different aetiological entity—possibly a form of chronic jejunitis.

Professor Douglas Hubble said that more than 50 jejunal biopsies had been done at the Birmingham Children's Hospital, and more than 30 of them in patients with established coeliac disease. In all but one of those with coeliac disease the mucosa was flattened, and the exception was a coeliac patient who had been on a strict gluten-free diet for 18 months before the biopsy. The second group described by Dr. Fone showed a lesion not encountered at the Children's Hospital. There was a small group of children with steatorrhoea in whom the coeliac change had not been demonstrated, and in some of these the cause of steatorrhoea was not established. There was some evidence that in coeliac disease the intestinal lesion might be reversed by a gluten-free diet.

Dr. R. H. Girdwood had carried out similar investigations in conjunction with Dr. I.W. Delamore and Dr. A. Wynn Williams. Of 22 adult patients with 'idiopathic steatorrhoea', nine had flattening of the mucosa, and the villi were almost absent (group I); five of these had malabsorption of vitamin B_{12}, while eight had malabsorption of folic acid. There were nine patients with abnormal villi (group II), and of these five had malabsorption of vitamin B_{12}, while six had malabsorption of folic acid. Four patients with 'idiopathic steatorrhoea' had a normal mucosal pattern, and of these one had been on a gluten-free diet. He felt that there was as yet insufficient evidence to justify the application of the term 'adult coeliac disease' only to patients with absent villi, or to all such cases. One of his own patients with symptoms from early childhood had type II changes. On the other hand, he thought that the present terminology was unsatisfactory, and this particularly applied to the use of the name 'malabsorption syndrome' for conditions in which the clinical features varied so greatly. He asked, too, whether the xylose absorption tests were done over a period of only five hours, since in his experience a significant proportion of xylose may be excreted in the urine after five hours.

Dr. J. Badenoch said that until more was known about the sensitivity to gluten in the two groups of patients described, he thought they should not be divided categorically into two entirely separate entities. It might be wiser to start with the response to a gluten-free diet, and see whether there were histological differences between those that responded and those that did not.

Dr. P. Fourman asked whether there were any differences between the two groups of patients in the absorption or metabolism of calcium.

Dr. J. W. Paulley thought that on the present evidence it was premature to define so decisively two diseases. He was reminded of a recent attempt to attribute different aetiologies to the various forms of ulcerative colitis. Coeliac disease and idiopathic steatorrhoea had variable aetiologies. Three of these—emotional stress, the toxic effect of inadequately digested gluten, and inflammation—had so far been reported as important, and variations in morbid histology should be expected, depending on the site of attack and the severity of each of these factors.

In reply, DR. FONE agreed that serial biopsies before and after treatment were necessary to prove whether or not significant change did occur in individual patients—especially in those with a 'flat' biopsy, but he stressed the fact that in their patients with a 'flat' biopsy the appearances were similar regardless of whether the patient was in relapse or remission (either spontaneous or as a result of a gluten-free diet). Only single specimens were obtained at any one time, but in those in whom second biopsies had been performed the appearances remained essentially unchanged. Eleven patients with a 'flat' biopsy had been treated with a gluten-free diet, and all eight who adhered to the diet responded well. Of 10 patients with 'abnormal villi' treated with the diet, seven responded well or moderately well. There were three failures in this group despite strict adherence to the diet. He did not agree with the concept of gluten-induced enteropathy as a separate entity, and pointed out that a gluten-free diet almost certainly had a non-specific as well as a specific effect. The different histological patterns seemed a sound basis on which to subdivide this group of disorders, and the clinical and laboratory features correlated well. It was difficult to explain the different incidence of anaemia on the basis of the two groups being merely stages of one underlying disease. The xylose absorption tests were performed on a five-hour collection. Disorders of calcium metabolism were present in both groups, but more common in the group with 'flat' biopsy; this finding was at present being more fully studied with investigation of the plasma-calcium fractions.

12. DR. A. GOLDBERG (introduced by PROFESSOR E. J. WAYNE) discussed *Radio-iron and Radiochromium Techniques as a Guide to the Management of Haemolytic and Aplastic Anaemias and Myeloproliferative Disease*. In acquired haemolytic anaemia splenectomy was usually stated to be advantageous in about half the cases, but, in order to predict its value in an individual patient, sequestration studies using radiochromium (^{51}Cr) were performed on 18 patients with idiopathic acquired haemolytic anaemia. A splenic: liver ratio of radioactivity at $t\frac{1}{2}$ (i.e. half-life of the radiochromium-labelled erythrocytes) of 2·4 or more to 1 was found to be a satisfactory indication for splenectomy, which had been carried out in six of these patients, with excellent results in each case. The radiochromium techniques were also useful in detecting a haemolytic element in hypoplastic anaemias, and steroid therapy had been of value in two patients in whom a haemolytic element existed. It was also important to determine the indications for splenectomy in myeloproliferative diseases. Eight patients with myelofibrosis or myelosclerosis had been investigated with radio-iron (^{59}Fe) and radiochromium (^{51}Cr) techniques, and the role of the spleen assessed. Splenectomy was indicated when there was a marked haemolytic anaemia requiring frequent blood transfusions, and when the spleen was mainly a site of blood destruction and showed little evidence of extramedullary erythropoiesis. One patient had an atypically situated spleen which presented a 'problem abdominal mass'. The radio-isotopic investigations in this case afforded a correct diagnosis of the mass. Since these results were not possible by the use of conventional methods of investigation, it was concluded that radio-iron and radiochromium techniques were of practical value in the management of these blood disorders.

DR. R. H. GIRDWOOD agreed that these investigations were sometimes essential for accurate diagnosis, and as a guide to treatment, particularly in cases in which atypical haemolytic anaemia might be misdiagnosed as aplastic anaemia. Many workers, especially surgeons, had become interested in treating aplastic anaemia by destroying immunity reactions with X-rays or chemotherapeutic agents and then doing marrow transplants. If such treatment were contemplated, the diagnosis would have to be absolutely certain, and confirmed by modern investigative methods. He wondered whether, in referring to haemolysis in aplastic anaemia, DR. GOLDBERG meant true aplastic anaemia with a haemolytic element, or haemolytic anaemia that had been misdiagnosed as aplastic anaemia.

DR. RICHARD ASHER said that the cases had been separated into those in which the spleen was destroying blood and should therefore be removed, and those in which it was making blood and should therefore be kept. Had there been instances where isotope studies showed that both processes were occurring simultaneously? He also inquired how close was the correlation between these predictions from radioactivity and the results of splenectomy.

PROFESSOR L. J. WITTS inquired whether patients had been operated on in whom the tests suggested that the operation might not be successful. His own experience had been that the results of splenectomy were sometimes at variance with the results of the tests.

DR. T. A. J. PRANKERD agreed with PROFESSOR WITTS about the difficulty of predicting the value of splenectomy from isotope studies, and wondered why a spleen: liver ratio of

2·4 had been chosen as a criterion for operation. He had found that the pattern of splenic iron uptake altered if corrections were made for the isotope circulating in red cells through the spleen.

In reply, DR. GOLDBERG agreed with DR. GIRDWOOD that it might be impossible to differentiate between predominant hypoplasia with haemolysis and predominant haemolysis with hypoplasia. He gave further details of the two patients in whom steroid therapy had proved of value. There were two patients with myelofibrosis in whom the spleen showed evidence of erythrocyte sequestration and also of extramedullary erythropoiesis. In such cases, if frequent blood transfusions were necessary, it was likely that the haemolytic activity of the spleen was the predominant factor, and that splenectomy would be of value, but each case demanded an individual appraisal. In the patient with myelofibrosis in whom splenectomy had been successful, there had been as yet, one year after the operation, no significant enlargement of the liver. The radio-iron studies had not been repeated, but the repetition of the radiochromium studies had shown an improvement of the $t\frac{1}{2}$ from 14 days, before operation, to 28 days after operation. In reply to DR. ASHER, PROFESSOR WITTS, and DR. PRANKERD, he said that the selection of the splenic : liver ratio at $t\frac{1}{2}$ of 2·4 : 1 as a dividing line had been empirical, but guided by the previous studies of Jandl and Schloesser. This ratio of 2·4 : 1 was well above those of the normal group, and also of the group with splenomegaly and a normal erythrocyte life-span. In retrospect, all six patients with idiopathic acquired haemolytic anaemia who had been operated upon had improved, and the $t\frac{1}{2}$ ^{51}Cr had risen in each case. In addition, three further patients had had a successful splenectomy, recommended on the basis of the radio-isotopic findings. Each of these nine patients had a splenic : liver ratio greater than 2·4 : 1. In the literature of the past 12 years 53 patients with acquired haemolytic anaemia had improved, out of 101 patients who had had a splenectomy, without previous radio-isotopic investigations. In the present study nine patients had improved out of nine selected for splenectomy on the basis of the radiochromium investigations. This difference was statistically significant ($P < 0{\cdot}05$ and $> 0{\cdot}02$).

13. DR. R. F. MAHLER and DR. B. MCARDLE (introduced by PROFESSOR JOHN BUTTERFIELD) described a *Specific Enzyme Defect in Glycogen Breakdown Causing a Myopathy*. This disease manifested itself in childhood or early adolescence with pain, stiffness, and weakness in the muscles on moderate exertion ; on more severe exercise the affected muscles became rigid, hard, and extremely tender to the touch, sometimes for many hours. In two patients such episodes had at times been followed by transient myoglobinuria. Of the seven patients known to be affected, two were brother and sister ; the others were not related, nor were any of their relatives known to be suffering from any form of myopathy. The basis of this disorder was a deficiency of the enzyme phosphorylase in striated muscle. Lack of this enzyme prevented the rapid mobilization of glycogen, so that no lactic acid formed on exercise, and the absence of a rise in the blood lactic-acid concentration after exercise was a diagnostic biochemical feature. The muscles could utilize glucose, and the supply of this substance was greatly assisted by the very high muscle blood-flow associated with exercise in this condition. The supply of glucose could also be increased therapeutically by raising the blood-sugar level or by the injection of insulin. Alternatively fructose, which was easily metabolized by the muscle, could be given, conveniently and effectively as 'invert sugar' or honey. Patients report that, within 30 minutes of taking this sugar, they are able to perform tasks which they had not been able to do before.

PROFESSOR SIR ROBERT PLATT said that the disorder could be the homozygous expression of a single gene, and noted that in one of the recorded cases a brother and sister were affected. He asked whether the other cases had any sibs, and whether any studies of relatives had been made which might detect the defect in its heterozygous form.

DR. E. M. BUZZARD asked whether the symptoms were always symmetrical and bilateral, because he had seen a patient referred for intermittent claudication in whom the vascular system was normal and the symptoms, which affected only the left leg, were similar to those described by DR. MAHLER. This particular patient was much troubled by night cramps in both legs.

PROFESSOR D. K. O'DONOVAN asked whether insulin sensitivity had been studied in these patients, and DR. HELEN DIMSDALE inquired whether one patient, who had muscle wasting, had shown any increase in serum aldolase. PROFESSOR F. J. NATTRASS said this beautiful work was the first demonstration of a specific enzyme defect in a primary muscle disorder. It raised the hope that a similar discovery might be made in the common dystrophies.

In reply, DR. MAHLER said that, except for the brother and sister mentioned, none of the patients' relatives were known to be suffering from any kind of myopathy, and that ischaemic forearm exercise produced a normal rise in the blood lactic-acid levels in those patients' relatives in whom this test had been done. There were no known diabetics among the relatives, but insulin sensitivity tests had not been done on either the patients or their relatives. Some enzyme levels had been measured in three patients and found to be normal, including the one patient in whom there was some muscle wasting. He thought it possible that the enzyme defect might be limited to certain muscles, but proof of this would depend on the biochemical or histochemical demonstration of the absence of the enzyme in the affected muscles.

14. DR. C. T. DOLLERY, DR. J. B. WEST (introduced), and DR. P. HUGH-JONES described *The Distribution of Pulmonary Blood-Flow in some Cases of Heart Disease as demonstrated by Oxygen-15*. The radioactive isotope of oxygen (^{15}O), which has a half-life of only two minutes, had been prepared in the Medical Research Council's cyclotron at Hammersmith Hospital. Using this isotope to label carbon dioxide, as $C^{15}O_2$, regional lung function was studied without the need to intubate patients. Scintillation counters were aligned in front of and behind the chest, and the radioactivity coming from a core of lung tissue between the counters was measured after a single breath containing a trace of the active gas. Since carbon dioxide is highly diffusible, the decline in counting rate during breath-holding, as the radioactive gas was cleared from the core of lung tissue by the blood, was used as a measure of the local blood-flow. In normal subjects sitting upright the $C^{15}O_2$ clearance rate was about three times as great in the lower zones of the lungs as in the upper zones. In patients with mitral stenosis this difference was often abolished, and in severe cases the difference was reversed so that the flow in the upper zones was greater than that in the lower. Some patients with auricular and ventricular septal defect showed that in both these conditions clearance in the upper zones was often the same as that in the lower zones. One boy with a ventricular septal defect was found to have an upper-zone clearance four times that in the lower zones, and in this respect to be like a patient with severe mitral stenosis. In him the $C^{15}O_2$ studies agreed qualitatively with the distribution of blood as shown by angiography, and at operation he was shown in fact to have mitral stenosis as well as the septal defect. In many patients with septal defect a left-to-right shunt was demonstrated on the $C^{15}O_2$ clearance curves, as secondary peaks during the decline of radioactivity in the breath-holding period, when shunted blood re-entered the counting field.

DR. LAWSON MCDONALD asked whether the velocity as well as the volume of pulmonary blood-flow per minute determined the clearance rate of $C^{15}O_2$. DR. J. M. BISHOP asked whether measurements had been made on patients with essential pulmonary hypertension or with septal defects and secondary pulmonary hypertension, and whether a similar distribution of blood-flow was found to that in mitral stenosis. DR. P. C. REYNELL said the abnormal distribution of blood-flow looked like a mechanism to protect the lower lobes against pulmonary oedema, and asked whether this distribution was modified by recumbency. DR. G. DE J. LEE asked whether the small variations shown on the clearance curves were in time with the cardiac cycle and represented pulsatile flow in the lungs.

In reply, DR. HUGH-JONES said that experiments were being done to determine what factors determined the clearance rates of carbon dioxide and other gases labelled with ^{15}O. No measurements had yet been made in essential pulmonary hypertension; some patients with septal defects, with and without pulmonary hypertension, were at present being studied, and showed the abolition of the normal increase of flow from upper to lower zones, but not the marked reversal seen in mitral stenosis. The effect of posture on the distribution of blood-flow in the lungs was of great interest, and its effects, like those of exercise, would have to be studied, but there were technical difficulties with the present equipment, and proper studies would have to wait until the heavy pairs of counters could be moved with the patient into a horizontal position. Finally, the small variations shown in the counting rate during the general decline in the breath-holding period were not synchronous with the electrocardiogram.

After an excellent luncheon provided most generously by the Medical College, members and their wives were guests of the Right Honourable Viscount Simon, C.M.G., Chairman of the Port of London Authority, for a voyage down the river in the Steam Yacht *St. Katharine*.

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